

Docket No.: 797



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE PATENT APPLICATION TRANSMITTAL UNDER 37 CFR 1.53



BOX PATENT APPLICATION Assistant Commissioner for Patents Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s):

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Tom Wehrman, Radoje T. Drmanac

Title:

NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

1. Type of application

- This is a new application for a
 - Utility patent.
 - Design patent.
- Applicants claim small entity status (See 37 CFR 1.27) Х

2. **Application Papers Enclosed**

- 1 Title Page
- 142 Pages of Specification (excluding Claims, Abstract, Drawings & Sequence Listing)
- Page(s) of Claims 4
- Page(s) of Abstract 1
- 0 Sheet(s) of Drawings (Figs. X-X)
- Formal
- ☐ Informal

723 Page(s) of Sequence Listing

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Patent Application Transmittal and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on November 17, 2000, in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Labet No EK415382545US

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4.

3. Oath or Declaration

	Enclosed					
		Executed by (check all applicable boxes)				
		Inventor(s)				
		Legal representative of inventors(s) (37 CFR 1.42 or 1.43)				
		Joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached				
		The petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 are enclosed. See Item 5D below for fee.				
X	Unexecuted – the undersigned attorney or agent is authorized to file this application on behalf of the applicant(s). An executed declaration will follow.					
Additi	Additional Papers Enclosed					
	Prelim	inary Amendment				
	Information Disclosure Statement					
	Declaration of Biological Deposit					
X	Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence					
X	Statement Under 37 CFR § 1.821					
x	Paper copy of sequence listing identical to computer copy (723 pages)					
	Microfiche computer program					
	Associate Power of Attorney					
	Verifie	d translation of a non-English patent application				
x	Return receipt postcard					
	Other					
Priority Applications Under 35 USC 119						
Certified copies of applications from which priority under 35 USC 119 is claimed are listed below and						
		are attached.				
		will follow.				

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5.

6. Filing Fee Calculation (37 CFR 1.16)

A. x Utility Application

CLAIMS AS FILED – INCLUDING PRELIMINARY AMENDMENT (IF ANY)								
,				LENTITY	OTHER THAN A SMALL ENTITY			
	NO. FILED	NO. EXTRA	RATE	FEE	RATE	FEE		
BASIC FEE	[83]]			\$355.00	200	\$710.00		
TOTAL	30-20	= 10	X 9=	\$90.00	X 18=	\$0.00		
INDEP.	3-3	= 0	X 40 =	\$00.00	X 80 =	\$0.00		
Γ First Presenta	tion of Multiple D	Dependent Claim	+ 135 =	\$135.00	+ 270 =	\$0.00		
		FIL	\$580.00	OR	\$0.00			

В.		Design Application (\$160.00/\$320.00) Filing Fee: \$	S				
C.		Plant Application (\$245.00/\$490.00) Filing Fee: \$	8				
D.	Other	Other fees					
		Recording Assignment [Fee \$40.00 per assignment]	\$				
		Petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached [Fee \$130.00]	\$				
		Other	\$				

TOTAL FEES ENCLOSED \$ 580.00

7. Method of Payments of Fees

- □ Enclosed check
- x Charge Deposit Account No. 501169. A duplicate copy of this transmittal is enclosed
- □ Not enclosed

8. Deposit Account and Refund Authorization

The Commissioner is hereby authorized to charge payment of any additional fees due or credit any overpayment to Deposit Account No. 501169. A duplicate copy of this transmittal is enclosed.

Please refund any overpayment to Hyseq, Inc. at the address below.

Please direct all future correspondence to Leslie A. Mooi at the address below.

Respectfully submitted,

Date: November 17, 2000

By:

Leslie A. Mooi

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Our Ref. No.: 797

NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

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NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

1. BACKGROUND OF THE INVENTION

5 1.1 TECHNICAL FIELD

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with uses for these polynucleotides and proteins, for example in therapeutic, diagnostic and research methods.

10 1.2 BACKGROUND

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs, chemokines, and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization-based cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity, for example, by virtue of their secreted nature in the case of leader sequence cloning, by virtue of their cell or tissue source in the case of PCR-based techniques, or by virtue of structural similarity to other genes of known biological activity.

Identified polynucleotide and polypeptide sequences have numerous applications in, for example, diagnostics, forensics, gene mapping; identification of mutations responsible for genetic disorders or other traits, to assess biodiversity, and to produce many other types of data and products dependent on DNA and amino acid sequences.

2. SUMMARY OF THE INVENTION

The compositions of the present invention include novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies.

The compositions of the present invention additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides.

The present invention relates to a collection or library of at least one novel nucleic acid sequence assembled from expressed sequence tags (ESTs) isolated mainly by sequencing by hybridization (SBH), and in some cases, sequences obtained from one or more public databases. The invention relates also to the proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins. These nucleic acid sequences are designated as SEQ ID NO: 1 – 362 and are provided in the Sequence Listing. In the nucleic acids provided in the Sequence Listing, A is adenosine; C is cytosine; G is guanine; T is thymine; and N is any of the four bases. In the amino acids provided in the Sequence Listing, * corresponds to the stop codon.

The nucleic acid sequences of the present invention also include, nucleic acid sequences that hybridize to the complement of SEQ ID NO: 1-362 under stringent hybridization conditions; nucleic acid sequences which are allelic variants or species homologues of any of the nucleic acid sequences recited above, or nucleic acid sequences that encode a peptide comprising a specific domain or truncation of the peptides encoded by SEQ ID NO: 1-362. A polynucleotide comprising a nucleotide sequence having at least 90% identity to an identifying sequence of SEQ ID NO: 1-362 or a degenerate variant or fragment thereof. The identifying sequence can be 100 base pairs in length.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO: 1-362. The sequence

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information can be a segment of any one of SEQ ID NO: 1-362 that uniquely identifies or represents the sequence information of SEQ ID NO: 1-362.

A collection as used in this application can be a collection of only one polynucleotide. The collection of sequence information or identifying information of each sequence can be provided on a nucleic acid array. In one embodiment, segments of sequence information is provided on a nucleic acid array to detect the polynucleotide that contains the segment. The array can be designed to detect full-match or mismatch to the polynucleotide that contains the segment. The collection can also be provided in a computer-readable format.

This invention also includes the reverse or direct complement of any of the nucleic acid sequences recited above; cloning or expression vectors containing the nucleic acid sequences; and host cells or organisms transformed with these expression vectors. Nucleic acid sequences (or their reverse or direct complements) according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology, such as use as hybridization probes, use as primers for PCR, use in an array, use in computer-readable media, use in sequencing full-length genes, use for chromosome and gene mapping, use in the recombinant production of protein, and use in the generation of anti-sense DNA or RNA, their chemical analogs and the like.

In a preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-362 or novel segments or parts of the nucleic acids of the invention are used as primers in expression assays that are well known in the art. In a particularly preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-362 or novel segments or parts of the nucleic acids provided herein are used in diagnostics for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The isolated polynucleotides of the invention include, but are not limited to, a polynucleotide comprising any one of the nucleotide sequences set forth in SEQ ID NO: 1–362; a polynucleotide comprising any of the full length protein coding sequences of SEQ ID NO: 1–362; and a polynucleotide comprising any of the nucleotide sequences of the mature protein coding sequences of SEQ ID NO: 1–362. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under

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stringent hybridization conditions to (a) the complement of any one of the nucleotide sequences set forth in SEQ ID NO: 1–362; (b) a nucleotide sequence encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotides recited above; (d) a polynucleotide which encodes a species homolog (e.g. orthologs) of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of any of the polypeptides comprising an amino acid sequence set forth in the Sequence Listing.

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising any of the amino acid sequences set forth in the Sequence Listing; or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides with biological activity that are encoded by (a) any of the polynucleotides having a nucleotide sequence set forth in SEQ ID NO: 1-362; or (b) polynucleotides that hybridize to the complement of the polynucleotides of (a) under stringent hybridization conditions. Biologically or immunologically active variants of any of the polypeptide sequences in the Sequence Listing, and "substantial equivalents" thereof (e.g., with at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid sequence identity) that preferably retain biological activity are also contemplated. The polypeptides of the invention may be wholly or partially chemically synthesized but are preferably produced by recombinant means using the genetically engineered cells (e.g. host cells) of the invention.

The invention also provides compositions comprising a polypeptide of the invention. Polypeptide compositions of the invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The invention also provides host cells transformed or transfected with a polynucleotide of the invention.

The invention also relates to methods for producing a polypeptide of the invention comprising growing a culture of the host cells of the invention in a suitable culture medium under conditions permitting expression of the desired polypeptide, and purifying the polypeptide from the culture or from the host cells. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Polynucleotides according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology. These

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techniques include use as hybridization probes, use as oligomers, or primers, for PCR, use for chromosome and gene mapping, use in the recombinant production of protein, and use in generation of anti-sense DNA or RNA, their chemical analogs and the like. For example, when the expression of an mRNA is largely restricted to a particular cell or tissue type, polynucleotides of the invention can be used as hybridization probes to detect the presence of the particular cell or tissue mRNA in a sample using, *e.g.*, *in situ* hybridization.

In other exemplary embodiments, the polynucleotides are used in diagnostics as expressed sequence tags for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The polypeptides according to the invention can be used in a variety of conventional procedures and methods that are currently applied to other proteins. For example, a polypeptide of the invention can be used to generate an antibody that specifically binds the polypeptide. Such antibodies, particularly monoclonal antibodies, are useful for detecting or quantitating the polypeptide in tissue. The polypeptides of the invention can also be used as molecular weight markers, and as a food supplement.

Methods are also provided for preventing, treating, or ameliorating a medical condition which comprises the step of administering to a mammalian subject a therapeutically effective amount of a composition comprising a polypeptide of the present invention and a pharmaceutically acceptable carrier.

In particular, the polypeptides and polynucleotides of the invention can be utilized, for example, in methods for the prevention and/or treatment of disorders involving aberrant protein expression or biological activity.

The present invention further relates to methods for detecting the presence of the polynucleotides or polypeptides of the invention in a sample. Such methods can, for example, be utilized as part of prognostic and diagnostic evaluation of disorders as recited herein and for the identification of subjects exhibiting a predisposition to such conditions. The invention provides a method for detecting the polynucleotides of the invention in a sample, comprising contacting the sample with a compound that binds to and forms a complex with the polynucleotide of interest for a period sufficient to form

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the complex and under conditions sufficient to form a complex and detecting the complex such that if a complex is detected, the polynucleotide of interest is detected. The invention also provides a method for detecting the polypeptides of the invention in a sample comprising contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex and detecting the formation of the complex such that if a complex is formed, the polypeptide is detected.

The invention also provides kits comprising polynucleotide probes and/or monoclonal antibodies, and optionally quantitative standards, for carrying out methods of the invention. Furthermore, the invention provides methods for evaluating the efficacy of drugs, and monitoring the progress of patients, involved in clinical trials for the treatment of disorders as recited above.

The invention also provides methods for the identification of compounds that modulate (i.e., increase or decrease) the expression or activity of the polynucleotides and/or polypeptides of the invention. Such methods can be utilized, for example, for the identification of compounds that can ameliorate symptoms of disorders as recited herein. Such methods can include, but are not limited to, assays for identifying compounds and other substances that interact with (*e.g.*, bind to) the polypeptides of the invention. The invention provides a method for identifying a compound that binds to the polypeptides of the invention comprising contacting the compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and detecting the complex by detecting the reporter gene sequence expression such that if expression of the reporter gene is detected the compound the binds to a polypeptide of the invention is identified.

The methods of the invention also provides methods for treatment which involve the administration of the polynucleotides or polypeptides of the invention to individuals exhibiting symptoms or tendencies. In addition, the invention encompasses methods for treating diseases or disorders as recited herein comprising administering compounds and other substances that modulate the overall activity of the target gene products.

Compounds and other substances can effect such modulation either on the level of target gene/protein expression or target protein activity.

The polypeptides of the present invention and the polynucleotides encoding them are also useful for the same functions known to one of skill in the art as the polypeptides and polynucleotides to which they have homology (set forth in Table 1); for which they have a signature region (as set forth in Table 3); or for which they have homology to a gene family (as set forth in Table 4). If no homology is set forth for a sequence, then the polypeptides and polynucleotides of the present invention are useful for a variety of applications, as described herein, including use in arrays for detection.

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3. DETAILED DESCRIPTION OF THE INVENTION

3.1 DEFINITIONS

It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

The term "active" refers to those forms of the polypeptide which retain the biologic and/or immunologic activities of any naturally occurring polypeptide. According to the invention, the terms "biologically active" or "biological activity" refer to a protein or peptide having structural, regulatory or biochemical functions of a naturally occurring molecule. Likewise "immunologically active" or "immunological activity" refers to the capability of the natural, recombinant or synthetic polypeptide to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The term "activated cells" as used in this application are those cells which are engaged in extracellular or intracellular membrane trafficking, including the export of secretory or enzymatic molecules as part of a normal or disease process.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence 5'-AGT-3' binds to the complementary sequence 3'-TCA-5'. Complementarity between two single-stranded molecules may be "partial" such that only some of the nucleic acids bind or it may be "complete" such that total complementarity exists between the single stranded molecules.

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The degree of complementarity between the nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands.

The term "embryonic stem cells (ES)" refers to a cell that can give rise to many differentiated cell types in an embryo or an adult, including the germ cells. The term "germ line stem cells (GSCs)" refers to stem cells derived from primordial stem cells that provide a steady and continuous source of germ cells for the production of gametes. The term "primordial germ cells (PGCs)" refers to a small population of cells set aside from other cell lineages particularly from the yolk sac, mesenteries, or gonadal ridges during embryogenesis that have the potential to differentiate into germ cells and other cells. PGCs are the source from which GSCs and ES cells are derived. The PGCs, the GSCs and the ES cells are capable of self-renewal. Thus these cells not only populate the germ line and give rise to a plurality of terminally differentiated cells that comprise the adult specialized organs, but are able to regenerate themselves.

The term "expression modulating fragment," EMF, means a series of nucleotides which modulates the expression of an operably linked ORF or another EMF.

As used herein, a sequence is said to "modulate the expression of an operably linked sequence" when the expression of the sequence is altered by the presence of the EMF. EMFs include, but are not limited to, promoters, and promoter modulating sequences (inducible elements). One class of EMFs are nucleic acid fragments which induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

The terms "nucleotide sequence" or "nucleic acid" or "polynucleotide" or "oligonculeotide" are used interchangeably and refer to a heteropolymer of nucleotides or the sequence of these nucleotides. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. In the sequences herein A is adenine, C is cytosine, T is thymine, G is guanine and N is A, C, G or T (U). It is contemplated that where the polynucleotide is RNA, the T (thymine) in the sequences provided herein is substituted with U (uracil). Generally, nucleic acid segments provided by this invention may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of

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oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid which is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon, or a eukaryotic gene.

The terms "oligonucleotide fragment" or a "polynucleotide fragment", "portion," or "segment" or "probe" or "primer" are used interchangeably and refer to a sequence of nucleotide residues which are at least about 5 nucleotides, more preferably at least about 7 nucleotides, more preferably at least about 9 nucleotides, more preferably at least about 11 nucleotides and most preferably at least about 17 nucleotides. The fragment is preferably less than about 500 nucleotides, preferably less than about 200 nucleotides, more preferably less than about 100 nucleotides, more preferably less than about 50 nucleotides and most preferably less than 30 nucleotides. Preferably the probe is from about 6 nucleotides to about 200 nucleotides, preferably from about 15 to about 50 nucleotides, more preferably from about 17 to 30 nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can be used in polymerase chain reaction (PCR), various hybridization procedures or microarray procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A fragment or segment may uniquely identify each polynucleotide sequence of the present invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ ID NOs:1-362.

Probes may, for example, be used to determine whether specific mRNA molecules are present in a cell or tissue or to isolate similar nucleic acid sequences from chromosomal DNA as described by Walsh et al. (Walsh, P.S. et al., 1992, PCR Methods Appl 1:241-250). They may be labeled by nick translation, Klenow fill-in reaction, PCR, or other methods well known in the art. Probes of the present invention, their preparation and/or labeling are elaborated in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY; or Ausubel, F.M. et al., 1989, Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, both of which are incorporated herein by reference in their entirety.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NOs: 1-362. The sequence information can be a segment of any one of SEQ ID NOs: 1-362 that uniquely identifies

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or represents the sequence information of that sequence of SEQ ID NO: 1-362. One such segment can be a twenty-mer nucleic acid sequence because the probability that a twenty-mer is fully matched in the human genome is 1 in 300. In the human genome, there are three billion base pairs in one set of chromosomes. Because 4²⁰ possible twenty-mers exist, there are 300 times more twenty-mers than there are base pairs in a set of human chromosomes. Using the same analysis, the probability for a seventeen-mer to be fully matched in the human genome is approximately 1 in 5. When these segments are used in arrays for expression studies, fifteen-mer segments can be used. The probability that the fifteen-mer is fully matched in the expressed sequences is also approximately one in five because expressed sequences comprise less than approximately 5% of the entire genome sequence.

Similarly, when using sequence information for detecting a single mismatch, a segment can be a twenty-five mer. The probability that the twenty-five mer would appear in a human genome with a single mismatch is calculated by multiplying the probability for a full match $(1 \div 4^{25})$ times the increased probability for mismatch at each nucleotide position (3×25) . The probability that an eighteen mer with a single mismatch can be detected in an array for expression studies is approximately one in five. The probability that a twenty-mer with a single mismatch can be detected in a human genome is approximately one in five.

The term "open reading frame," ORF, means a series of nucleotide triplets coding for amino acids without any termination codons and is a sequence translatable into protein.

The terms "operably linked" or "operably associated" refer to functionally related nucleic acid sequences. For example, a promoter is operably associated or operably linked with a coding sequence if the promoter controls the transcription of the coding sequence. While operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements e.g. repressor genes are not contiguously linked to the coding sequence but still control transcription/translation of the coding sequence.

The term "pluripotent" refers to the capability of a cell to differentiate into a number of differentiated cell types that are present in an adult organism. A pluripotent cell is restricted in its differentiation capability in comparison to a totipotent cell.

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The terms "polypeptide" or "peptide" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or synthetic molecules. A polypeptide "fragment," "portion," or "segment" is a stretch of amino acid residues of at least about 5 amino acids, preferably at least about 7 amino acids, more preferably at least about 9 amino acids and most preferably at least about 17 or more amino acids. The peptide preferably is not greater than about 200 amino acids, more preferably less than 150 amino acids and most preferably less than 100 amino acids. Preferably the peptide is from about 5 to about 200 amino acids. To be active, any polypeptide must have sufficient length to display biological and/or immunological activity.

The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation.

The term "translated protein coding portion" means a sequence which encodes for the full length protein which may include any leader sequence or any processing sequence.

The term "mature protein coding sequence" means a sequence which encodes a peptide or protein without a signal or leader sequence. The "mature protein portion" means that portion of the protein which does not include a signal or leader sequence. The peptide may have been produced by processing in the cell which removes any leader/signal sequence. The mature protein portion may or may not include the initial methionine residue. The methionine residue may be removed from the protein during processing in the cell. The peptide may be produced synthetically or the protein may have been produced using a polynucleotide only encoding for the mature protein coding sequence.

The term "derivative" refers to polypeptides chemically modified by such techniques as ubiquitination, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol)

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and insertion or substitution by chemical synthesis of amino acids such as ornithine, which do not normally occur in human proteins.

The term "variant" (or "analog") refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions, created using, *e.g.*, recombinant DNA techniques. Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, may be found by comparing the sequence of the particular polypeptide with that of homologous peptides and minimizing the number of amino acid sequence changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence.

Alternatively, recombinant variants encoding these same or similar polypeptides may be synthesized or selected by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes which produce various restriction sites, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic system. Mutations in the polynucleotide sequence may be reflected in the polypeptide or domains of other peptides added to the polypeptide to modify the properties of any part of the polypeptide, to change characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate.

Preferably, amino acid "substitutions" are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, *i.e.*, conservative amino acid replacements. "Conservative" amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophobicity, hydrophobicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. "Insertions" or "deletions" are preferably in the range of about 1 to 20 amino acids, more preferably 1 to 10 amino acids. The variation allowed may be experimentally determined by systematically making insertions,

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deletions, or substitutions of amino acids in a polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity.

Alternatively, where alteration of function is desired, insertions, deletions or non-conservative alterations can be engineered to produce altered polypeptides. Such alterations can, for example, alter one or more of the biological functions or biochemical characteristics of the polypeptides of the invention. For example, such alterations may change polypeptide characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate. Further, such alterations can be selected so as to generate polypeptides that are better suited for expression, scale up and the like in the host cells chosen for expression. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

The terms "purified" or "substantially purified" as used herein denotes that the indicated nucleic acid or polypeptide is present in the substantial absence of other biological macromolecules, *e.g.*, polynucleotides, proteins, and the like. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight, more preferably at least 99% by weight, of the indicated biological macromolecules present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 daltons, can be present).

The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one other component (e.g., nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the nucleic acid or polypeptide is found in the presence of (if anything) only a solvent, buffer, ion, or other component normally present in a solution of the same. The terms "isolated" and "purified" do not encompass nucleic acids or polypeptides present in their natural source.

The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (*e.g.*, microbial, insect, or mammalian) expression systems. "Microbial" refers to recombinant polypeptides or proteins made in bacterial or fungal (e.g., yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially free of native endogenous substances and unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, *e.g.*, *E. coli*, will be free of

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glycosylation modifications; polypeptides or proteins expressed in yeast will have a glycosylation pattern in general different from those expressed in mammalian cells.

The term "recombinant expression vehicle or vector" refers to a plasmid or phage or virus or vector, for expressing a polypeptide from a DNA (RNA) sequence. An expression vehicle can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an amino terminal methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final product.

The term "recombinant expression system" means host cells which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit extrachromosomally. Recombinant expression systems as defined herein will express heterologous polypeptides or proteins upon induction of the regulatory elements linked to the DNA segment or synthetic gene to be expressed. This term also means host cells which have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express polypeptides or proteins endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "secreted" includes a protein that is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence when it is expressed in a suitable host cell. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins that are transported across the membrane of the endoplasmic reticulum. "Secreted"

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proteins are also intended to include proteins containing non-typical signal sequences (e.g. Interleukin-1 Beta, see Krasney, P.A. and Young, P.R. (1992) Cytokine 4(2):134 -143) and factors released from damaged cells (e.g. Interleukin-1 Receptor Antagonist, see Arend, W.P. et. al. (1998) Annu. Rev. Immunol. 16:27-55)

Where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell. Such a sequence may be naturally present on the polypeptides of the present invention or provided from heterologous protein sources by recombinant DNA techniques.

The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Stringent conditions can include highly stringent conditions (i.e., hybridization to filter-bound DNA in 0.5 M NaHPO₄, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1X SSC/0.1% SDS at 68°C), and moderately stringent conditions (i.e., washing in 0.2X SSC/0.1% SDS at 42°C). Other exemplary hybridization conditions are described herein in the examples.

In instances of hybridization of deoxyoligonucleotides, additional exemplary stringent hybridization conditions include washing in 6X SSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligonucleotides), 48°C (for 17-base oligos), 55°C (for 20-base oligonucleotides), and 60°C (for 23-base oligonucleotides).

As used herein, "substantially equivalent" can refer both to nucleotide and amino acid sequences, for example a mutant sequence, that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences. Typically, such a substantially equivalent sequence varies from one of those listed herein by no more than about 35% (*i.e.*, the number of individual residue substitutions, additions, and/or deletions in a substantially equivalent sequence, as compared to the corresponding reference sequence, divided by the total number of residues in the substantially equivalent sequence is about 0.35 or less). Such a sequence is said to have 65% sequence identity to the listed sequence. In one embodiment, a substantially equivalent, *e.g.*, mutant, sequence of the invention varies from a listed sequence by no more than 30% (70% sequence identity); in a variation of this embodiment, by no more than 25% (75% sequence identity); and in a further variation of this embodiment, by no

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more than 20% (80% sequence identity) and in a further variation of this embodiment, by no more than 10% (90% sequence identity) and in a further variation of this embodiment, by no more that 5% (95% sequence identity). Substantially equivalent, e.g., mutant, amino acid sequences according to the invention preferably have at least 80% sequence identity with a listed amino acid sequence, more preferably at least 90% sequence identity. Substantially equivalent nucleotide sequences of the invention can have lower percent sequence identities, taking into account, for example, the redundancy or degeneracy of the genetic code. Preferably, nucleotide sequence has at least about 65% identity, more preferably at least about 75% identity, and most preferably at least about 95% identity. For the purposes of the present invention, sequences having substantially equivalent biological activity and substantially equivalent expression characteristics are considered substantially equivalent. For the purposes of determining equivalence, truncation of the mature sequence (e.g., via a mutation which creates a spurious stop codon) should be disregarded. Sequence identity may be determined, e.g., using the Jotun Hein method (Hein, J. (1990) Methods Enzymol. 183:626-645). Identity between sequences can also be determined by other methods known in the art, e.g. by varying hybridization conditions.

The term "totipotent" refers to the capability of a cell to differentiate into all of the cell types of an adult organism.

The term "transformation" means introducing DNA into a suitable host cell so that the DNA is replicable, either as an extrachromosomal element, or by chromosomal integration. The term "transfection" refers to the taking up of an expression vector by a suitable host cell, whether or not any coding sequences are in fact expressed. The term "infection" refers to the introduction of nucleic acids into a suitable host cell by use of a virus or viral vector.

As used herein, an "uptake modulating fragment," UMF, means a series of nucleotides which mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified using known UMFs as a target sequence or target motif with the computer-based systems described below. The presence and activity of a UMF can be confirmed by attaching the suspected UMF to a marker sequence. The resulting nucleic acid molecule is then incubated with an appropriate host under appropriate conditions and

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the uptake of the marker sequence is determined. As described above, a UMF will increase the frequency of uptake of a linked marker sequence.

Each of the above terms is meant to encompass all that is described for each, unless the context dictates otherwise.

3.2 NUCLEIC ACIDS OF THE INVENTION

Nucleotide sequences of the invention are set forth in the Sequence Listing.

The isolated polynucleotides of the invention include a polynucleotide comprising the nucleotide sequences of SEQ ID NO: 1 - 362; a polynucleotide encoding any one of the peptide sequences of SEQ ID NO:1 - 362; and a polynucleotide comprising the nucleotide sequence encoding the mature protein coding sequence of the polynucleotides of any one of SEQ ID NO: 1 - 362. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent conditions to (a) the complement of any of the nucleotides sequences of SEQ ID NO: 1 - 362; (b) nucleotide sequences encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotide recited above; (d) a polynucleotide which encodes a species homolog of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of the polypeptides of SEQ ID NO: 1-362. Domains of interest may depend on the nature of the encoded polypeptide; e.g., domains in receptorlike polypeptides include ligand-binding, extracellular, transmembrane, or cytoplasmic domains, or combinations thereof; domains in immunoglobulin-like proteins include the variable immunoglobulin-like domains; domains in enzyme-like polypeptides include catalytic and substrate binding domains; and domains in ligand polypeptides include receptor-binding domains.

The polynucleotides of the invention include naturally occurring or wholly or partially synthetic DNA, e.g., cDNA and genomic DNA, and RNA, e.g., mRNA. The polynucleotides may include all of the coding region of the cDNA or may represent a portion of the coding region of the cDNA.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known

methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. Further 5' and 3' sequence can be obtained using methods known in the art. For example, full length cDNA or genomic DNA that corresponds to any of the polynucleotides of SEQ ID NO: 1 – 362 can be obtained by screening appropriate cDNA or genomic DNA libraries under suitable hybridization conditions using any of the polynucleotides of SEQ ID NO: 1 – 362 or a portion thereof as a probe. Alternatively, the polynucleotides of SEQ ID NO: 1 – 362 may be used as the basis for suitable primer(s) that allow identification and/or amplification of genes in appropriate genomic DNA or cDNA libraries.

The nucleic acid sequences of the invention can be assembled from ESTs and sequences (including cDNA and genomic sequences) obtained from one or more public databases, such as dbEST, gbpri, and UniGene. The EST sequences can provide identifying sequence information, representative fragment or segment information, or novel segment information for the full-length gene.

The polynucleotides of the invention also provide polynucleotides including nucleotide sequences that are substantially equivalent to the polynucleotides recited above. Polynucleotides according to the invention can have, *e.g.*, at least about 65%, at least about 70%, at least about 75%, at least about 80%, more typically at least about 90%, and even more typically at least about 95%, sequence identity to a polynucleotide recited above.

Included within the scope of the nucleic acid sequences of the invention are nucleic acid sequence fragments that hybridize under stringent conditions to any of the nucleotide sequences of SEQ ID NO: 1 - 362, or complements thereof, which fragment is greater than about 5 nucleotides, preferably 7 nucleotides, more preferably greater than 9 nucleotides and most preferably greater than 17 nucleotides. Fragments of, e.g. 15, 17, or 20 nucleotides or more that are selective for (i.e. specifically hybridize to any one of the polynucleotides of the invention) are contemplated. Probes capable of specifically hybridizing to a polynucleotide can differentiate polynucleotide sequences of the invention from other polynucleotide sequences in the same family of genes or can

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differentiate human genes from genes of other species, and are preferably based on unique nucleotide sequences.

The sequences falling within the scope of the present invention are not limited to these specific sequences, but also include allelic and species variations thereof. Allelic and species variations can be routinely determined by comparing the sequence provided in SEQ ID NO: 1 - 362, a representative fragment thereof, or a nucleotide sequence at least 90% identical, preferably 95% identical, to SEQ ID NOs: 1 - 362 with a sequence from another isolate of the same species. Furthermore, to accommodate codon variability, the invention includes nucleic acid molecules coding for the same amino acid sequences as do the specific ORFs disclosed herein. In other words, in the coding region of an ORF, substitution of one codon for another codon that encodes the same amino acid is expressly contemplated.

The nearest neighbor or homology result for the nucleic acids of the present invention, including SEQ ID NOs: 1 - 362, can be obtained by searching a database using an algorithm or a program. Preferably, a BLAST which stands for Basic Local Alignment Search Tool is used to search for local sequence alignments (Altshul, S.F. J Mol. Evol. 36 290-300 (1993) and Altschul S.F. et al. J. Mol. Biol. 21:403-410 (1990)). Alternatively a FASTA version 3 search against Genpept, using Fastxy algorithm.

Species homologs (or orthologs) of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

The nucleic acid sequences of the invention are further directed to sequences which encode variants of the described nucleic acids. These amino acid sequence variants may be prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant polynucleotide. There are two variables in the construction of amino acid sequence variants: the location of the mutation and the nature of the mutation. Nucleic acids encoding the amino acid sequence variants are preferably

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constructed by mutating the polynucleotide to encode an amino acid sequence that does not occur in nature. These nucleic acid alterations can be made at sites that differ in the nucleic acids from different species (variable positions) or in highly conserved regions (constant regions). Sites at such locations will typically be modified in series, e.g., by substituting first with conservative choices (e.g., hydrophobic amino acid to a different hydrophobic amino acid) and then with more distant choices (e.g., hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be made at the target site. Amino acid sequence deletions generally range from about 1 to 30 residues, preferably about 1 to 10 residues, and are typically contiguous. Amino acid insertions include amino- and/or carboxyl-terminal fusions ranging in length from one to one hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of terminal insertions include the heterologous signal sequences necessary for secretion or for intracellular targeting in different host cells and sequences such as FLAG or poly-histidine sequences useful for purifying the expressed protein.

In a preferred method, polynucleotides encoding the novel amino acid sequences are changed via site-directed mutagenesis. This method uses oligonucleotide sequences to alter a polynucleotide to encode the desired amino acid variant, as well as sufficient adjacent nucleotides on both sides of the changed amino acid to form a stable duplex on either side of the site of being changed. In general, the techniques of site-directed mutagenesis are well known to those of skill in the art and this technique is exemplified by publications such as, Edelman et al., *DNA* 2:183 (1983). A versatile and efficient method for producing site-specific changes in a polynucleotide sequence was published by Zoller and Smith, *Nucleic Acids Res.* 10:6487-6500 (1982). PCR may also be used to create amino acid sequence variants of the novel nucleic acids. When small amounts of template DNA are used as starting material, primer(s) that differs slightly in sequence from the corresponding region in the template DNA can generate the desired amino acid variant. PCR amplification results in a population of product DNA fragments that differ from the polynucleotide template encoding the polypeptide at the position specified by

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the primer. The product DNA fragments replace the corresponding region in the plasmid and this gives a polynucleotide encoding the desired amino acid variant.

A further technique for generating amino acid variants is the cassette mutagenesis technique described in Wells et al., *Gene* 34:315 (1985); and other mutagenesis techniques well known in the art, such as, for example, the techniques in Sambrook et al., supra, and *Current Protocols in Molecular Biology*, Ausubel et al. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be used in the practice of the invention for the cloning and expression of these novel nucleic acids. Such DNA sequences include those which are capable of hybridizing to the appropriate novel nucleic acid sequence under stringent conditions.

Polynucleotides encoding preferred polypeptide truncations of the invention can be used to generate polynucleotides encoding chimeric or fusion proteins comprising one or more domains of the invention and heterologous protein sequences.

The polynucleotides of the invention additionally include the complement of any of the polynucleotides recited above. The polynucleotide can be DNA (genomic, cDNA, amplified, or synthetic) or RNA. Methods and algorithms for obtaining such polynucleotides are well known to those of skill in the art and can include, for example, methods for determining hybridization conditions that can routinely isolate polynucleotides of the desired sequence identities.

In accordance with the invention, polynucleotide sequences comprising the mature protein coding sequences corresponding to any one of SEQ ID NO: 1-362, or functional equivalents thereof, may be used to generate recombinant DNA molecules that direct the expression of that nucleic acid, or a functional equivalent thereof, in appropriate host cells. Also included are the cDNA inserts of any of the clones identified herein.

A polynucleotide according to the invention can be joined to any of a variety of other nucleotide sequences by well-established recombinant DNA techniques (see Sambrook J et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY). Useful nucleotide sequences for joining to polynucleotides include an assortment of vectors, e.g., plasmids, cosmids, lambda phage derivatives, phagemids, and

the like, that are well known in the art. Accordingly, the invention also provides a vector including a polynucleotide of the invention and a host cell containing the polynucleotide. In general, the vector contains an origin of replication functional in at least one organism, convenient restriction endonuclease sites, and a selectable marker for the host cell.

Vectors according to the invention include expression vectors, replication vectors, probe generation vectors, and sequencing vectors. A host cell according to the invention can be a prokaryotic or eukaryotic cell and can be a unicellular organism or part of a multicellular organism.

The present invention further provides recombinant constructs comprising a nucleic acid having any of the nucleotide sequences of SEQ ID NOs: 1 - 362 or a fragment thereof or any other polynucleotides of the invention. In one embodiment, the recombinant constructs of the present invention comprise a vector, such as a plasmid or viral vector, into which a nucleic acid having any of the nucleotide sequences of SEQ ID NOs: 1 - 362 or a fragment thereof is inserted, in a forward or reverse orientation. In the case of a vector comprising one of the ORFs of the present invention, the vector may further comprise regulatory sequences, including for example, a promoter, operably linked to the ORF. Large numbers of suitable vectors and promoters are known to those of skill in the art and are commercially available for generating the recombinant constructs of the present invention. The following vectors are provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, PXTI, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia).

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al., *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the

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protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, and trc. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), a-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an amino terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product. Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include E. coli, Bacillus subtilis, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived

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from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM 1 (Promega Biotech, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced or derepressed by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Polynucleotides of the invention can also be used to induce immune responses. For example, as described in Fan et al., *Nat. Biotech.* 17:870-872 (1999), incorporated herein by reference, nucleic acid sequences encoding a polypeptide may be used to generate antibodies against the encoded polypeptide following topical administration of naked plasmid DNA or following injection, and preferably intramuscular injection of the DNA. The nucleic acid sequences are preferably inserted in a recombinant expression vector and may be in the form of naked DNA.

3.3 HOSTS

The present invention further provides host cells genetically engineered to contain the polynucleotides of the invention. For example, such host cells may contain nucleic acids of the invention introduced into the host cell using known transformation, transfection or infection methods. The present invention still further provides host cells genetically engineered to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell.

Knowledge of nucleic acid sequences allows for modification of cells to permit, or increase, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the polypeptide at higher levels. The heterologous

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promoter is inserted in such a manner that it is operatively linked to the encoding sequences. See, for example, PCT International Publication No. WO94/12650, PCT International Publication No. WO92/20808, and PCT International Publication No. WO91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

The host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated transfection, or electroporation (Davis, L. et al., *Basic Methods in Molecular Biology* (1986)). The host cells containing one of the polynucleotides of the invention, can be used in conventional manners to produce the gene product encoded by the isolated fragment (in the case of an ORF) or can be used to produce a heterologous protein under the control of the EMF.

Any host/vector system can be used to express one or more of the ORFs of the present invention. These include, but are not limited to, eukaryotic hosts such as HeLa cells, Cv-1 cell, COS cells, 293 cells, and Sf9 cells, as well as prokaryotic host such as *E. coli* and *B. subtilis*. The most preferred cells are those which do not normally express the particular polypeptide or protein or which expresses the polypeptide or protein at low natural level. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., in Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, New York (1989), the disclosure of which is hereby incorporated by reference.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7

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lines of monkey kidney fibroblasts, described by Gluzman, Cell 23:175 (1981). Other cell lines capable of expressing a compatible vector are, for example, the C127, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Recombinant polypeptides and proteins produced in bacterial culture are usually isolated by initial extraction from cell pellets, followed by one or more salting-out, aqueous ion exchange or size exclusion chromatography steps. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or insects or in prokaryotes such as bacteria. Potentially suitable yeast strains include Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces strains, Candida, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include Escherichia coli, Bacillus subtilis, Salmonella typhimurium, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the

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invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequence include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, e.g., inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the host cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this

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purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

3.4 POLYPEPTIDES OF THE INVENTION

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising: the amino acid sequences set forth as any one of SEQ ID NO: 1-362 or an amino acid sequence encoded by any one of the nucleotide sequences SEQ ID NOs: 1 - 362 or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides preferably with biological or immunological activity that are encoded by: (a) a polynucleotide having any one of the nucleotide sequences set forth in SEQ ID NOs: 1 - 362 or (b) polynucleotides encoding any one of the amino acid sequences set forth as SEQ ID NO: 1-362 or (c) polynucleotides that hybridize to the complement of the polynucleotides of either (a) or (b) under stringent hybridization conditions. The invention also provides biologically active or immunologically active variants of any of the amino acid sequences set forth as SEQ ID NO: 1-362 or the corresponding full length or mature protein; and "substantial equivalents" thereof (e.g., with at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, typically at least about 95%, more typically at least about 98%, or most typically at least about 99% amino acid identity) that retain biological activity. Polypeptides encoded by allelic variants may have a similar, increased, or decreased activity compared to polypeptides comprising SEQ ID NO: 1-362.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for

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example, as described in H. U. Saragovi, et al., Bio/Technology 10, 773-778 (1992) and in R. S. McDowell, et al., J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites.

The present invention also provides both full-length and mature forms (for example, without a signal sequence or precursor sequence) of the disclosed proteins. The protein coding sequence is identified in the sequence listing by translation of the disclosed nucleotide sequences. The mature form of such protein may be obtained by expression of a full-length polynucleotide in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein is also determinable from the amino acid sequence of the full-length form. Where proteins of the present invention are membrane bound, soluble forms of the proteins are also provided. In such forms, part or all of the regions causing the proteins to be membrane bound are deleted so that the proteins are fully secreted from the cell in which they are expressed.

Protein compositions of the present invention may further comprise an acceptable carrier, such as a hydrophilic, *e.g.*, pharmaceutically acceptable, carrier.

The present invention further provides isolated polypeptides encoded by the nucleic acid fragments of the present invention or by degenerate variants of the nucleic acid fragments of the present invention. By "degenerate variant" is intended nucleotide fragments which differ from a nucleic acid fragment of the present invention (e.g., an ORF) by nucleotide sequence but, due to the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic acid fragments of the present invention are the ORFs that encode proteins.

A variety of methodologies known in the art can be utilized to obtain any one of the isolated polypeptides or proteins of the present invention. At the simplest level, the amino acid sequence can be synthesized using commercially available peptide synthesizers. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. This technique is particularly useful in producing small peptides and fragments

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of larger polypeptides. Fragments are useful, for example, in generating antibodies against the native polypeptide. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The polypeptides and proteins of the present invention can alternatively be purified from cells which have been altered to express the desired polypeptide or protein. As used herein, a cell is said to be altered to express a desired polypeptide or protein when the cell, through genetic manipulation, is made to produce a polypeptide or protein which it normally does not produce or which the cell normally produces at a lower level. One skilled in the art can readily adapt procedures for introducing and expressing either recombinant or synthetic sequences into eukaryotic or prokaryotic cells in order to generate a cell which produces one of the polypeptides or proteins of the present invention.

The invention also relates to methods for producing a polypeptide comprising growing a culture of host cells of the invention in a suitable culture medium, and purifying the protein from the cells or the culture in which the cells are grown. For example, the methods of the invention include a process for producing a polypeptide in which a host cell containing a suitable expression vector that includes a polynucleotide of the invention is cultured under conditions that allow expression of the encoded polypeptide. The polypeptide can be recovered from the culture, conveniently from the culture medium, or from a lysate prepared from the host cells and further purified. Preferred embodiments include those in which the protein produced by such process is a full length or mature form of the protein.

In an alternative method, the polypeptide or protein is purified from bacterial cells which naturally produce the polypeptide or protein. One skilled in the art can readily follow known methods for isolating polypeptides and proteins in order to obtain one of the isolated polypeptides or proteins of the present invention. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immuno-affinity chromatography. See, *e.g.*, Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag (1994); Sambrook, et al., in Molecular Cloning: *A Laboratory Manual*; Ausubel et al., *Current Protocols in*

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Molecular Biology. Polypeptide fragments that retain biological/immunological activity include fragments comprising greater than about 100 amino acids, or greater than about 200 amino acids, and fragments that encode specific protein domains.

The purified polypeptides can be used in *in vitro* binding assays which are well known in the art to identify molecules which bind to the polypeptides. These molecules include but are not limited to, for e.g., small molecules, molecules from combinatorial libraries, antibodies or other proteins. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

In addition, the peptides of the invention or molecules capable of binding to the peptides may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for SEQ ID NO: 1-362.

The protein of the invention may also be expressed as a product of transgenic animals, *e.g.*, as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications, in the peptide or DNA sequence, can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, *e.g.*, U.S. Pat. No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein. Regions of the protein that are important for the protein function can be determined by various methods known in

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the art including the alanine-scanning method which involved systematic substitution of single or strings of amino acids with alanine, followed by testing the resulting alanine-containing variant for biological activity. This type of analysis determines the importance of the substituted amino acid(s) in biological activity. Regions of the protein that are important for protein function may be determined by the eMATRIX program.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and are useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are encompassed by the present invention.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, Calif., U.S.A. (the MaxBatTM kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearlTM or Cibacrom blue 3GA SepharoseTM; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin

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(TRX), or as a His tag. Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, Mass.), Pharmacia (Piscataway, N.J.) and Invitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("FLAG®") is commercially available from Kodak (New Haven,

One such epitope ("FLAG®") is commercially available from Kodak (New Haven, Conn.).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The polypeptides of the invention include analogs (variants). This embraces fragments, as well as peptides in which one or more amino acids has been deleted, inserted, or substituted. Also, analogs of the polypeptides of the invention embrace fusions of the polypeptides or modifications of the polypeptides of the invention, wherein the polypeptide or analog is fused to another moiety or moieties, e.g., targeting moiety or another therapeutic agent. Such analogs may exhibit improved properties such as activity and/or stability. Examples of moieties which may be fused to the polypeptide or an analog include, for example, targeting moieties which provide for the delivery of polypeptide to pancreatic cells, e.g., antibodies to pancreatic cells, antibodies to immune cells such as T-cells, monocytes, dendritic cells, granulocytes, etc., as well as receptor and ligands expressed on pancreatic or immune cells. Other moieties which may be fused to the polypeptide include therapeutic agents which are used for treatment, for example, immunosuppressive drugs such as cyclosporin, SK506, azathioprine, CD3 antibodies and steroids. Also, polypeptides may be fused to immune modulators, and other cytokines such as alpha or beta interferon.

3.4.1 DETERMINING POLYPEPTIDE AND POLYNUCLEOTIDE IDENTITY AND SIMILARITY

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Preferred identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in computer programs including, but are not limited to, the GCG program package, including GAP (Devereux, J., et al., Nucleic Acids Research 12(1):387 (1984); Genetics 5 Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, BLASTX, FASTA (Altschul, S.F. et al., J. Molec. Biol. 215:403-410 (1990), PSI-BLAST (Altschul S.F. et al., Nucleic Acids Res. vol. 25, pp. 3389-3402, herein incorporated by reference), eMatrix software (Wu et al., J. Comp. Biol., Vol. 6, pp. 219-235 (1999), herein incorporated by reference), eMotif software (Nevill-Manning et al, ISMB-97, Vol. 4, pp. 202-209, herein incorporated by reference), pFam software (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1), pp. 320-322 (1998), herein incorporated by reference) and the Kyte-Doolittle hydrophobocity prediction algorithm (J. Mol Biol, 157, pp. 105-31 (1982), incorporated herein by reference). The BLAST programs are publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul, S., et al. NCB NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990).

3.5 GENE THERAPY

Mutations in the polynucleotides of the invention gene may result in loss of normal function of the encoded protein. The invention thus provides gene therapy to restore normal activity of the polypeptides of the invention; or to treat disease states involving polypeptides of the invention. Delivery of a functional gene encoding polypeptides of the invention to appropriate cells is effected ex vivo, in situ, or in vivo by use of vectors, and more particularly viral vectors (e.g., adenovirus, adeno-associated virus, or a retrovirus), or ex vivo by use of physical DNA transfer methods (e.g., liposomes or chemical treatments). See, for example, Anderson, Nature, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, Science, 244: 1275-1281 (1989); Verma, Scientific American: 68-84 (1990); and Miller, Nature, 357: 455-460 (1992). Introduction of any one of the nucleotides of the present invention or a gene encoding the polypeptides of the present invention can also be accomplished with extrachromosomal substrates (transient

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expression) or artificial chromosomes (stable expression). Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes. Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

Other methods inhibiting expression of a protein include the introduction of antisense molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in the art. Further, the polypeptides of the present invention can be inhibited by using targeted deletion methods, or the insertion of a negative regulatory element such as a silencer, which is tissue specific.

The present invention still further provides cells genetically engineered *in vivo* to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell. These methods can be used to increase or decrease the expression of the polynucleotides of the present invention.

Knowledge of DNA sequences provided by the invention allows for modification of cells to permit, increase, or decrease, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the protein at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the desired protein encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the desired

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protein coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences.

Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, *e.g.*, inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting

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sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

3.6 TRANSGENIC ANIMALS

In preferred methods to determine biological functions of the polypeptides of the invention in vivo, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of a promoter of the polynucleotides of the invention is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased

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protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

The polynucleotides of the present invention also make possible the development, through, e.g., homologous recombination or knock out strategies, of animals that fail to express polypeptides of the invention or that express a variant polypeptide. Such animals are useful as models for studying the *in vivo* activities of polypeptide as well as for studying modulators of the polypeptides of the invention.

In preferred methods to determine biological functions of the polypeptides of the invention *in vivo*, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of the polynucleotides of the invention promoter is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

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3.7 USES AND BIOLOGICAL ACTIVITY

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The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA). The mechanism underlying the particular condition or pathology will dictate whether the polypeptides of the invention, the polynucleotides of the invention or modulators (activators or inhibitors) thereof would be beneficial to the subject in need of treatment. Thus, "therapeutic compositions of the invention" include compositions comprising isolated polynucleotides (including recombinant DNA molecules, cloned genes and degenerate variants thereof) or polypeptides of the invention (including full length protein, mature protein and truncations or domains thereof), or compounds and other substances that modulate the overall activity of the target gene products, either at the level of target gene/protein expression or target protein activity. Such modulators include polypeptides, analogs, (variants), including fragments and fusion proteins, antibodies and other binding proteins; chemical compounds that directly or indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); antisense polynucleotides and polynucleotides suitable for triple helix formation; and in particular antibodies or other binding partners that specifically recognize one or more epitopes of the polypeptides of the invention.

The polypeptides of the present invention may likewise be involved in cellular activation or in one of the other physiological pathways described herein.

3.7.1 RESEARCH USES AND UTILITIES

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on gels; as chromosome markers or tags (when

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labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding polypeptide is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology:

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Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

3.7.2 NUTRITIONAL USES

Polynucleotides and polypeptides of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the polypeptide or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the polypeptide or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

3.7.3 CYTOKINE AND CELL PROLIFERATION/DIFFERENTIATION ACTIVITY

A polypeptide of the present invention may exhibit activity relating to cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of therapeutic compositions of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e, CMK, HUVEC, and Caco. Therapeutic compositions of the invention can be used in the following:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19;

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Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., I. Immunol. 149:3778-3783, 1992; Bowman et al., I. Immunol. 152:1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A. M. and Shevach, E. M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human interleukin-γ, Schreiber, R. D. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L. S. and Lipsky, P. E. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6--Nordan, R. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Aced. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11--Bennett, F., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9--Ciarletta, A., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H.

Margulies, E. M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter

6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

3.7.4 STEM CELL GROWTH FACTOR ACTIVITY

A polypeptide of the present invention may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells, hematopoietic stem cells and/or germ line stem cells. Administration of the polypeptide of the invention to stem cells in vivo or ex vivo is expected to maintain and expand cell populations in a totipotential or pluripotential state which would be useful for reengineering damaged or diseased tissues, transplantation, manufacture of biopharmaceuticals and the development of bio-sensors. The ability to produce large quantities of human cells has important working applications for the production of human proteins which currently must be obtained from non-human sources or donors, implantation of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow, skin, cartilage, tendons, bone, muscle (including cardiac muscle), blood vessels, cornea, neural cells, gastrointestinal cells and others; and organs for transplantation such as kidney, liver, pancreas (including islet cells), heart and lung.

It is contemplated that multiple different exogenous growth factors and/or cytokines may be administered in combination with the polypeptide of the invention to achieve the desired effect, including any of the growth factors listed herein, other stem cell maintenance factors, and specifically including stem cell factor (SCF), leukemia inhibitory factor (LIF), Flt-3 ligand (Flt-3L), any of the interleukins, recombinant soluble IL-6 receptor fused to IL-6, macrophage inflammatory protein 1-alpha (MIP-1-alpha), G-CSF, GM-CSF, thrombopoietin (TPO), platelet factor 4 (PF-4), platelet-derived growth factor (PDGF), neural growth factors and basic fibroblast growth factor (bFGF).

Since totipotent stem cells can give rise to virtually any mature cell type, expansion of these cells in culture will facilitate the production of large quantities of

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mature cells. Techniques for culturing stem cells are known in the art and administration of polypeptides of the invention, optionally with other growth factors and/or cytokines, is expected to enhance the survival and proliferation of the stem cell populations. This can be accomplished by direct administration of the polypeptide of the invention to the culture medium. Alternatively, stroma cells transfected with a polynucleotide that encodes for the polypeptide of the invention can be used as a feeder layer for the stem cell populations in culture or in vivo. Stromal support cells for feeder layers may include embryonic bone marrow fibroblasts, bone marrow stromal cells, fetal liver cells, or cultured embryonic fibroblasts (see U.S. Patent No. 5,690,926).

Stem cells themselves can be transfected with a polynucleotide of the invention to induce autocrine expression of the polypeptide of the invention. This will allow for generation of undifferentiated totipotential/pluripotential stem cell lines that are useful as is or that can then be differentiated into the desired mature cell types. These stable cell lines can also serve as a source of undifferentiated totipotential/pluripotential mRNA to create cDNA libraries and templates for polymerase chain reaction experiments. These studies would allow for the isolation and identification of differentially expressed genes in stem cell populations that regulate stem cell proliferation and/or maintenance.

Expansion and maintenance of totipotent stem cell populations will be useful in the treatment of many pathological conditions. For example, polypeptides of the present invention may be used to manipulate stem cells in culture to give rise to neuroepithelial cells that can be used to augment or replace cells damaged by illness, autoimmune disease, accidental damage or genetic disorders. The polypeptide of the invention may be useful for inducing the proliferation of neural cells and for the regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders which involve degeneration, death or trauma to neural cells or nerve tissue. In addition, the expanded stem cell populations can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or implantation.

Expression of the polypeptide of the invention and its effect on stem cells can also be manipulated to achieve controlled differentiation of the stem cells into more differentiated cell types. A broadly applicable method of obtaining pure populations of a

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specific differentiated cell type from undifferentiated stem cell populations involves the use of a cell-type specific promoter driving a selectable marker. The selectable marker allows only cells of the desired type to survive. For example, stem cells can be induced to differentiate into cardiomyocytes (Wobus et al., Differentiation, 48: 173-182, (1991); Klug et al., J. Clin. Invest., 98(1): 216-224, (1998)) or skeletal muscle cells (Browder, L. W. In: *Principles of Tissue Engineering eds.* Lanza et al., Academic Press (1997)). Alternatively, directed differentiation of stem cells can be accomplished by culturing the stem cells in the presence of a differentiation factor such as retinoic acid and an antagonist of the polypeptide of the invention which would inhibit the effects of endogenous stem cell factor activity and allow differentiation to proceed.

In vitro cultures of stem cells can be used to determine if the polypeptide of the invention exhibits stem cell growth factor activity. Stem cells are isolated from any one of various cell sources (including hematopoietic stem cells and embryonic stem cells) and cultured on a feeder layer, as described by Thompson et al. Proc. Natl. Acad. Sci, U.S.A., 92: 7844-7848 (1995), in the presence of the polypeptide of the invention alone or in combination with other growth factors or cytokines. The ability of the polypeptide of the invention to induce stem cells proliferation is determined by colony formation on semi-solid support e.g. as described by Bernstein et al., Blood, 77: 2316-2321 (1991).

3.7.5 HEMATOPOIESIS REGULATING ACTIVITY

A polypeptide of the present invention may be involved in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell disorders. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation

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of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

Therapeutic compositions of the invention can be used in the following:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M. G. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I. K. and Briddell, R. A. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, N.Y. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R. E. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, N.Y. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R. I.

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Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, N.Y. 1994; Long term culture initiating cell assay, Sutherland, H. J. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, N.Y. 1994.

3.7.6 TISSUE GROWTH ACTIVITY

A polypeptide of the present invention also may be involved in bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as in wound healing and tissue repair and replacement, and in healing of burns, incisions and ulcers.

A polypeptide of the present invention which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Compositions of a polypeptide, antibody, binding partner, or other modulator of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A polypeptide of this invention may also be involved in attracting bone-forming cells, stimulating growth of bone-forming cells, or inducing differentiation of progenitors of bone-forming cells. Treatment of osteoporosis, osteoarthritis, bone degenerative disorders, or periodontal disease, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes may also be possible using the composition of the invention.

Another category of tissue regeneration activity that may involve the polypeptide of the present invention is tendon/ligament formation. Induction of tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue.

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De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The compositions of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a composition may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a composition of the invention.

Compositions of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

Compositions of the present invention may also be involved in the generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising

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such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring may allow normal tissue to regenerate. A polypeptide of the present invention may also exhibit angiogenic activity.

A composition of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A composition of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Therapeutic compositions of the invention can be used in the following:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H. I. and Rovee, D. T., eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

3.7.7 IMMUNE STIMULATING OR SUPPRESSING ACTIVITY

A polypeptide of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A polynucleotide of the invention can encode a polypeptide exhibiting such activities. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpes

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viruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, proteins of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein (or antagonists thereof, including antibodies) of the present invention may also to be useful in the treatment of allergic reactions and conditions (e.g., anaphylaxis, serum sickness, drug reactions, food allergies, insect venom allergies, mastocytosis, allergic rhinitis, hypersensitivity pneumonitis, urticaria, angioedema, eczema, atopic dermatitis, allergic contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, allergic conjunctivitis, atopic keratoconjunctivitis, venereal keratoconjunctivitis, giant papillary conjunctivitis and contact allergies), such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein (or antagonists thereof) of the present invention. The therapeutic effects of the polypeptides or antagonists thereof on allergic reactions can be evaluated by in vivo animals models such as the cumulative contact enhancement test (Lastbom et al., Toxicology 125: 59-66, 1998), skin prick test (Hoffmann et al., Allergy 54: 446-54, 1999), guinea pig skin sensitization test (Vohr et al., Arch. Toxocol. 73: 501-9), and murine local lymph node assay (Kimber et al., J. Toxicol. Environ. Health 53: 563-79).

Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent.

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Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a therapeutic composition of the invention may prevent cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, a lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular therapeutic compositions in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of therapeutic compositions of the invention on the development of that disease.

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Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block stimulation of T cells can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (e.g., a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response may be useful in cases of viral infection, including systemic viral diseases such as influenza, the common cold, and encephalitis.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected

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cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

A polypeptide of the present invention may provide the necessary stimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient mounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I alpha chain protein and β_2 microglobulin protein or an MHC class II alpha chain protein and an MHC class II beta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., I. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bowman et al., J. Virology 61:1992-1998; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

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Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J. J. and Brunswick, M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

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3.7.8 ACTIVIN/INHIBIN ACTIVITY

A polypeptide of the present invention may also exhibit activin- or inhibin-related activities. A polynucleotide of the invention may encode a polypeptide exhibiting such characteristics. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a polypeptide of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, U.S. Pat. No. 4,798,885. A polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as, but not limited to, cows, sheep and pigs.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods.

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Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

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3.7.9 CHEMOTACTIC/CHEMOKINETIC ACTIVITY

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A polypeptide of the present invention may be involved in chemotactic or chemokinetic activity for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Chemotactic and chemokinetic receptor activation can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic compositions (e.g. proteins, antibodies, binding partners, or modulators of the invention) provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

Therapeutic compositions of the invention can be used in the following:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Marguiles, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

3.7.10 HEMOSTATIC AND THROMBOLYTIC ACTIVITY

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A polypeptide of the invention may also be involved in hemostatis or thrombolysis or thrombosis. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Compositions may be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A composition of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

Therapeutic compositions of the invention can be used in the following:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

3.7.11 CANCER DIAGNOSIS AND THERAPY

Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of polynucleotides or polypeptides of the invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention may indicate a hereditary risk of cancer, a precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

Cancer treatments promote tumor regression by inhibiting tumor cell proliferation, inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Therapeutic compositions of the invention may be effective in adult and pediatric oncology including in solid phase tumors/malignancies, locally advanced tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases,

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blood cell malignancies including multiple myeloma, acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma, tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Karposi's sarcoma.

Polypeptides, polynucleotides, or modulators of polypeptides of the invention (including inhibitors and stimulators of the biological activity of the polypeptide of the invention) may be administered to treat cancer. Therapeutic compositions can be administered in therapeutically effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the polypeptide or modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. The use of anti-cancer cocktails as a cancer treatment is routine. Anti-cancer drugs that are well known in the art and can be used as a treatment in combination with the polypeptide or modulator of the invention include: Actinomycin D, Aminoglutethimide, Asparaginase, Bleomycin, Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cis-DDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin, Daunorubicin HCl,

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Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide acetate (LHRH-releasing factor analog), Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine,

Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these individuals with therapeutically effective doses of the polypeptide of the invention to reduce the risk of developing cancers.

In vitro models can be used to determine the effective doses of the polypeptide of the invention as a potential cancer treatment. These *in vitro* models include proliferation assays of cultured tumor cells, growth of cultured tumor cells in soft agar (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wily-Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999), respectively. Suitable tumor cells lines are available, e.g. from American Type Tissue Culture Collection catalogs.

3.7.12 RECEPTOR/LIGAND ACTIVITY

A polypeptide of the present invention may also demonstrate activity as receptor, receptor ligand or inhibitor or agonist of receptor/ligand interactions. A polynucleotide of the invention can encode a polypeptide exhibiting such characteristics. Examples of

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such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley- Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

By way of example, the polypeptides of the invention may be used as a receptor for a ligand(s) thereby transmitting the biological activity of that ligand(s). Ligands may be identified through binding assays, affinity chromatography, dihybrid screening assays, BIAcore assays, gel overlay assays, or other methods known in the art.

Studies characterizing drugs or proteins as agonist or antagonist or partial agonists or a partial antagonist require the use of other proteins as competing ligands. The polypeptides of the present invention or ligand(s) thereof may be labeled by being coupled to radioisotopes, colorimetric molecules or a toxin molecules by conventional methods. ("Guide to Protein Purification" Murray P. Deutscher (ed) Methods in Enzymology Vol. 182 (1990) Academic Press, Inc. San Diego). Examples of radioisotopes include, but are not limited to, tritium and carbon-14. Examples of

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colorimetric molecules include, but are not limited to, fluorescent molecules such as fluorescamine, or rhodamine or other colorimetric molecules. Examples of toxins include, but are not limited, to ricin.

3.7.13 DRUG SCREENING

This invention is particularly useful for screening chemical compounds by using the novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques. The polypeptides or fragments employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between polypeptides of the invention or fragments and the agent being tested or examine the diminution in complex formation between the novel polypeptides and an appropriate cell line, which are well known in the art.

Sources for test compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of polypeptides of the invention include (1) inorganic and organic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms themselves.

Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally

occurring) variants thereof. For a review, see *Science* 282:63-68 (1998).

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Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., *Mol. Biotechnol.* 9(3):205-23 (1998); Hruby et al., *Curr Opin Chem Biol.* 1(1):114-19 (1997); Dorner et al., *Bioorg Med Chem*, 4(5):709-15 (1996) (alkylated dipeptides).

Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to bind a polypeptide of the invention. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

The binding molecules thus identified may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells such as radioisotopes. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for a polypeptide of the invention. Alternatively, the binding molecules may be complexed with imaging agents for targeting and imaging purposes.

3.7.14 ASSAY FOR RECEPTOR ACTIVITY

The invention also provides methods to detect specific binding of a polypeptide e.g. a ligand or a receptor. The art provides numerous assays particularly useful for identifying previously unknown binding partners for receptor polypeptides of the invention. For example, expression cloning using mammalian or bacterial cells, or dihybrid screening assays can be used to identify polynucleotides encoding binding partners. As another example, affinity chromatography with the appropriate immobilized polypeptide of the invention can be used to isolate polypeptides that recognize and bind

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polypeptides of the invention. There are a number of different libraries used for the identification of compounds, and in particular small molecules, that modulate (*i.e.*, increase or decrease) biological activity of a polypeptide of the invention. Ligands for receptor polypeptides of the invention can also be identified by adding exogenous ligands, or cocktails of ligands to two cells populations that are genetically identical except for the expression of the receptor of the invention: one cell population expresses the receptor of the invention whereas the other does not. The response of the two cell populations to the addition of ligands(s) are then compared. Alternatively, an expression library can be co-expressed with the polypeptide of the invention in cells and assayed for an autocrine response to identify potential ligand(s). As still another example, BIAcore assays, gel overlay assays, or other methods known in the art can be used to identify binding partner polypeptides, including, (1) organic and inorganic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

The role of downstream intracellular signaling molecules in the signaling cascade of the polypeptide of the invention can be determined. For example, a chimeric protein in which the cytoplasmic domain of the polypeptide of the invention is fused to the extracellular portion of a protein, whose ligand has been identified, is produced in a host cell. The cell is then incubated with the ligand specific for the extracellular portion of the chimeric protein, thereby activating the chimeric receptor. Known downstream proteins involved in intracellular signaling can then be assayed for expected modifications i.e. phosphorylation. Other methods known to those in the art can also be used to identify signaling molecules involved in receptor activity.

3.7.15 ANTI-INFLAMMATORY ACTIVITY

Compositions of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or

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promote an inflammatory response. Compositions with such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation intimation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Compositions of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material. Compositions of this invention may be utilized to prevent or treat conditions such as, but not limited to, sepsis, acute pancreatitis, endotoxin shock, cytokine induced shock, rheumatoid arthritis, chronic inflammatory arthritis, pancreatic cell damage from diabetes mellitus type 1, graft versus host disease, inflammatory bowel disease, inflammatory disease, an antiproliferative agent such as for acute or chronic mylegenous leukemia or in the prevention of premature labor secondary to intrauterine infections.

3.7.16 LEUKEMIAS

Leukemias and related disorders may be treated or prevented by administration of a therapeutic that promotes or inhibits function of the polynucleotides and/or polypeptides of the invention. Such leukemias and related disorders include but are not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia (for a review of such disorders, see Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia).

3.7.17 NERVOUS SYSTEM DISORDERS

Nervous system disorders, involving cell types which can be tested for efficacy of intervention with compounds that modulate the activity of the polynucleotides and/or polypeptides of the invention, and which can be treated upon thus observing an indication of therapeutic utility, include but are not limited to nervous system injuries, and diseases

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or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the invention include but are not limited to the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems:

- (i) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries;
- (ii) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia;
- (iii) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis;
- (iv) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis;
- (v) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration;
- (vi) neurological lesions associated with systemic diseases including but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis;
- (vii) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and
- 30 (viii) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including but not limited to multiple

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sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

Therapeutics which are useful according to the invention for treatment of a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, therapeutics which elicit any of the following effects may be useful according to the invention:

- (i) increased survival time of neurons in culture;
- (ii) increased sprouting of neurons in culture or in vivo;
- (iii) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or
 - (iv) decreased symptoms of neuron dysfunction in vivo.

Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may be measured by the method set forth in Arakawa et al. (1990, J. Neurosci. 10:3507-3515); increased sprouting of neurons may be detected by methods set forth in Pestronk et al. (1980, Exp. Neurol. 70:65-82) or Brown et al. (1981, Ann. Rev. Neurosci. 4:17-42); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, *etc.*, depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, *e.g.*, weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include but are not limited to disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including but not limited to progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive

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bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

3.7.18 OTHER ACTIVITIES

A polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, co-factors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

3.7.19 IDENTIFICATION OF POLYMORPHISMS

The demonstration of polymorphisms makes possible the identification of such polymorphisms in human subjects and the pharmacogenetic use of this information for diagnosis and treatment. Such polymorphisms may be associated with, e.g., differential predisposition or susceptibility to various disease states (such as disorders involving

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inflammation or immune response) or a differential response to drug administration, and this genetic information can be used to tailor preventive or therapeutic treatment appropriately. For example, the existence of a polymorphism associated with a predisposition to inflammation or autoimmune disease makes possible the diagnosis of this condition in humans by identifying the presence of the polymorphism.

Polymorphisms can be identified in a variety of ways known in the art which all generally involve obtaining a sample from a patient, analyzing DNA from the sample, optionally involving isolation or amplification of the DNA, and identifying the presence of the polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment of genomic DNA which may then be sequenced. Alternatively, the DNA may be subjected to allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides are hybridized to the DNA under conditions permitting detection of a single base mismatch) or to a single nucleotide extension assay (in which an oligonucleotide that hybridizes immediately adjacent to the position of the polymorphism is extended with one or more labeled nucleotides). In addition, traditional restriction fragment length polymorphism analysis (using restriction enzymes that provide differential digestion of the genomic DNA depending on the presence or absence of the polymorphism) may be performed. Arrays with nucleotide sequences of the present invention can be used to detect polymorphisms. The array can comprise modified nucleotide sequences of the present invention in order to detect the nucleotide sequences of the present invention. In the alternative, any one of the nucleotide sequences of the present invention can be placed on the array to detect changes from those sequences.

Alternatively a polymorphism resulting in a change in the amino acid sequence could also be detected by detecting a corresponding change in amino acid sequence of the protein, e.g., by an antibody specific to the variant sequence.

3.7.20 ARTHRITIS AND INFLAMMATION

The immunosuppressive effects of the compositions of the invention against rheumatoid arthritis is determined in an experimental animal model system. The experimental model system is adjuvant induced arthritis in rats, and the protocol is described by J. Holoshitz, et at., 1983, Science, 219:56, or by B. Waksman et al., 1963,

Int. Arch. Allergy Appl. Immunol., 23:129. Induction of the disease can be caused by a single injection, generally intradermally, of a suspension of killed Mycobacterium tuberculosis in complete Freund's adjuvant (CFA). The route of injection can vary, but rats may be injected at the base of the tail with an adjuvant mixture. The polypeptide is administered in phosphate buffered solution (PBS) at a dose of about 1-5 mg/kg. The control consists of administering PBS only.

The procedure for testing the effects of the test compound would consist of intradermally injecting killed Mycobacterium tuberculosis in CFA followed by immediately administering the test compound and subsequent treatment every other day until day 24. At 14, 15, 18, 20, 22, and 24 days after injection of Mycobacterium CFA, an overall arthritis score may be obtained as described by J. Holoskitz above. An analysis of the data would reveal that the test compound would have a dramatic affect on the swelling of the joints as measured by a decrease of the arthritis score.

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3.8 THERAPEUTIC METHODS

The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including antisense polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are not limited to, those exemplified herein.

3.8.1 EXAMPLE

One embodiment of the invention is the administration of an effective amount of the polypeptides or other composition of the invention to individuals affected by a disease or disorder that can be modulated by regulating the peptides of the invention. While the mode of administration is not particularly important, parenteral administration is preferred. An exemplary mode of administration is to deliver an intravenous bolus. The dosage of the polypeptides or other composition of the invention will normally be determined by the prescribing physician. It is to be expected that the dosage will vary according to the age, weight, condition and response of the individual patient. Typically,

the amount of polypeptide administered per dose will be in the range of about 0.01µg/kg to 100 mg/kg of body weight, with the preferred dose being about 0.1µg/kg to 10 mg/kg of patient body weight. For parenteral administration, polypeptides of the invention will be formulated in an injectable form combined with a pharmaceutically acceptable parenteral vehicle. Such vehicles are well known in the art and examples include water, saline, Ringer's solution, dextrose solution, and solutions consisting of small amounts of the human serum albumin. The vehicle may contain minor amounts of additives that maintain the isotonicity and stability of the polypeptide or other active ingredient. The preparation of such solutions is within the skill of the art.

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3.9 PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION

A protein or other composition of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources and including antibodies and other binding partners of the polypeptides of the invention) may be administered to a patient in need, by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a variety of disorders. Such a composition may optionally contain (in addition to protein or other active ingredient and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the disease or disorder in question. These agents include various growth factors such as epidermal growth factor (EGF),

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platelet-derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), insulin-like growth factor (IGF), as well as cytokines described herein.

The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or other active ingredient or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein or other active ingredient of the invention, or to minimize side effects. Conversely, protein or other active ingredient of the present invention may be included in formulations of the particular clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent (such as IL-1Ra, IL-1 Hy1, IL-1 Hy2, anti-TNF, corticosteroids, immunosuppressive agents). A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

As an alternative to being included in a pharmaceutical composition of the invention including a first protein, a second protein or a therapeutic agent may be concurrently administered with the first protein (e.g., at the same time, or at differing times provided that therapeutic concentrations of the combination of agents is achieved at the treatment site). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms, *e.g.*, treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

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In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein or other active ingredient of the present invention is administered to a mammal having a condition to be treated. Protein or other active ingredient of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When coadministered with one or more cytokines, lymphokines or other hematopoietic factors, protein or other active ingredient of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein or other active ingredient of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

3.9.1 ROUTES OF ADMINISTRATION

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Administration of protein or other active ingredient of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a arthritic joints or in fibrotic tissue, often in a depot or sustained release formulation. In order to prevent the scarring process frequently occurring as complication of glaucoma surgery, the compounds may be administered topically, for example, as eye drops. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome

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coated with a specific antibody, targeting, for example, arthritic or fibrotic tissue. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

The polypeptides of the invention are administered by any route that delivers an effective dosage to the desired site of action. The determination of a suitable route of administration and an effective dosage for a particular indication is within the level of skill in the art. Preferably for wound treatment, one administers the therapeutic compound directly to the site. Suitable dosage ranges for the polypeptides of the invention can be extrapolated from these dosages or from similar studies in appropriate animal models. Dosages can then be adjusted as necessary by the clinician to provide maximal therapeutic benefit.

3.9.2 COMPOSITIONS/FORMULATIONS

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of protein or other active ingredient of the present invention is administered orally, protein or other active ingredient of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein or other active ingredient of the present invention, and preferably from about 25 to 90% protein or other active ingredient of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol,

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propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein or other active ingredient of the present invention, and preferably from about 1 to 50% protein or other active ingredient of the present invention.

When a therapeutically effective amount of protein or other active ingredient of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein or other active ingredient of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein or other active ingredient solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein or other active ingredient of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose,

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hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or

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aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without

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destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose. Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein or other active ingredient stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Many of the active ingredients of the invention may be provided as salts with pharmaceutically compatible counter ions. Such pharmaceutically acceptable base addition salts are those salts which retain the biological effectiveness and properties of the free acids and which are obtained by reaction with inorganic or organic bases such as sodium hydroxide, magnesium hydroxide, ammonia, trialkylamine, dialkylamine, monoalkylamine, dibasic amino acids, sodium acetate, potassium benzoate, triethanol amine and the like.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) or other active ingredient(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T

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cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithins, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent Nos. 4,235,871; 4,501,728; 4,837,028; and 4,737,323, all of which are incorporated herein by reference.

The amount of protein or other active ingredient of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein or other active ingredient of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein or other active ingredient of the present invention and observe the patient's response.

Larger doses of protein or other active ingredient of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about $0.01~\mu g$ to about 100~m g (preferably about $0.1~\mu g$ to about 10~m g, more preferably about $0.1~\mu g$ to about 1~m g) of protein or other active ingredient of the present invention per kg body weight. For compositions of the present invention which are

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useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein or other active ingredient of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing or other active ingredient-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability. Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering

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agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells. In further compositions, proteins or other active ingredients of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins or other active ingredients of the present invention. The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, *e.g.*, amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final

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composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either in vivo or ex vivo into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA). Cells may also be cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes.

3.9.3 EFFECTIVE DOSAGE

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from appropriate in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that can be used to more accurately determine useful doses in humans. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC₅₀ as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the protein's biological activity). Such information can be used to more accurately determine useful doses in humans.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical

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procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀.

Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, *e.g.*, Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the desired effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

An exemplary dosage regimen for polypeptides or other compositions of the invention will be in the range of about $0.01~\mu g/kg$ to 100~mg/kg of body weight daily, with the preferred dose being about $0.1~\mu g/kg$ to 25~mg/kg of patient body weight daily, varying in adults and children. Dosing may be once daily, or equivalent doses may be delivered at longer or shorter intervals.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's age and weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

3.9.4 PACKAGING

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

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3.10 ANTIBODIES

Another aspect of the invention is an antibody that specifically binds the polypeptide of the invention. Such antibodies include monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR and/or antigen-binding sequences, which specifically recognize a polypeptide of the invention. Preferred antibodies of the invention are human antibodies which are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab', $F(ab')_2$, and F_v , are also provided by the invention. The term "specific for" indicates that the variable regions of the antibodies of the invention recognize and bind polypeptides of the invention exclusively (i.e., able to distinguish the polypeptide of the invention from other similar polypeptides despite sequence identity, homology, or similarity found in the family of polypeptides), but may also interact with other proteins (for example, S. aureus protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988),

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Chapter 6. Antibodies that recognize and bind fragments of the polypeptides of the invention are also contemplated, provided that the antibodies are first and foremost specific for, as defined above, full length polypeptides of the invention. As with antibodies that are specific for full length polypeptides of the invention, antibodies of the invention that recognize fragments are those which can distinguish polypeptides from the same family of polypeptides despite inherent sequence identity, homology, or similarity found in the family of proteins. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

Non-human antibodies may be humanized by any methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

Antibodies of the invention are useful for, for example, therapeutic purposes (by modulating activity of a polypeptide of the invention), diagnostic purposes to detect or quantitate a polypeptide of the invention, as well as purification of a polypeptide of the invention. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific. The invention further provides a hybridoma that produces an antibody according to the invention. Antibodies of the invention are useful for detection and/or purification of the polypeptides of the invention.

Polypeptides of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R. P. Merrifield, J. Amer. Chem. Soc. 85, 2149-2154 (1963); J. L. Krstenansky, et al., FEBS Lett. 211, 10 (1987).

Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions

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associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein. In general, techniques for preparing polyclonal and monoclonal antibodies as well as hybridomas capable of producing the desired antibody are well known in the art (Campbell, A.M., Monoclonal Antibodies Technology: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1984); St. Groth et al., J. Immunol. 35:1-21 (1990); Kohler and Milstein, Nature 256:495-497 (1975)), the trioma technique, the human B-cell hybridoma technique (Kozbor et al., Immunology Today 4:72 (1983); Cole et al., in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985), pp. 77-96).

Any animal (mouse, rabbit, etc.) which is known to produce antibodies can be immunized with a peptide or polypeptide of the invention. Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the polypeptide. One skilled in the art will recognize that the amount of the protein encoded by the ORF of the present invention used for immunization will vary based on the animal which is immunized, the antigenicity of the peptide and the site of injection. The protein that is used as an immunogen may be modified or administered in an adjuvant in order to increase the protein's antigenicity. Methods of increasing the antigenicity of a protein are well known in the art and include, but are not limited to, coupling the antigen with a heterologous protein (such as globulin or β -galactosidase) or through the inclusion of an adjuvant during immunization.

For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/0-Ag14 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells. Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, Western blot analysis, or radioimmunoassay (Lutz et al., Exp. Cell Research. 175:109-124 (1988)). Hybridomas secreting the desired antibodies are cloned and the class and subclass is determined using procedures known in the art (Campbell,

A.M., Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1984)). Techniques described for the production of single chain antibodies (U.S. Patent 4,946,778) can be adapted to produce single chain antibodies to proteins of the present invention.

For polyclonal antibodies, antibody-containing antiserum is isolated from the immunized animal and is screened for the presence of antibodies with the desired specificity using one of the above-described procedures. The present invention further provides the above- described antibodies in delectably labeled form. Antibodies can be delectably labeled through the use of radioisotopes, affinity labels (such as biotin, avidin, etc.), enzymatic labels (such as horseradish peroxidase, alkaline phosphatase, etc.) fluorescent labels (such as FITC or rhodamine, etc.), paramagnetic atoms, etc. Procedures for accomplishing such labeling are well-known in the art, for example, see (Sternberger, L.A. et al., J. Histochem. Cytochem. 18:315 (1970); Bayer, E.A. et al., Meth. Enzym. 62:308 (1979); Engval, E. et al., Immunol. 109:129 (1972); Goding, J.W. J. Immunol. Meth. 13:215 (1976)).

The labeled antibodies of the present invention can be used for *in vitro*, *in vivo*, and *in situ* assays to identify cells or tissues in which a fragment of the polypeptide of interest is expressed. The antibodies may also be used directly in therapies or other diagnostics. The present invention further provides the above-described antibodies immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and Sepharose®, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir, D.M. et al., "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10 (1986); Jacoby, W.D. et al., Meth. Enzym. 34 Academic Press, N.Y. (1974)). The immobilized antibodies of the present invention can be used for *in vitro*, *in vivo*, and *in situ* assays as well as for immuno-affinity purification of the proteins of the present invention.

3.11 COMPUTER READABLE SEQUENCES

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In one application of this embodiment, a nucleotide sequence of the present invention can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon a nucleotide sequence of the present invention. As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the nucleotide sequence information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (e.g. text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing any of the nucleotide sequences SEQ ID NOs: 1 - 362 or a representative fragment thereof; or a nucleotide sequence at least 95% identical to any of the nucleotide sequences of SEQ ID NOs: 1 - 362 in computer readable form, a skilled artisan can routinely access the sequence information for a variety of purposes.

Computer software is publicly available which allows a skilled artisan to access sequence

information provided in a computer readable medium. The examples which follow demonstrate how software which implements the BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et al., Comp. Chem. 17:203-207 (1993)) search algorithms on a Sybase system is used to identify open reading frames (ORFs) within a nucleic acid sequence. Such ORFs may be protein encoding fragments and may be useful in producing commercially important proteins such as enzymes used in fermentation reactions and in the production of commercially useful metabolites.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein a nucleotide sequence of the present invention and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store nucleotide sequence information of the present invention, or a memory access means which can access manufactures having recorded thereon the nucleotide sequence information of the present invention.

As used herein, "search means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of a known sequence which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. Examples of such software includes, but is not limited to, Smith-Waterman, MacPattern (EMBL), BLASTN and BLASTA (NPOLYPEPTIDEIA). A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting homology searches can be adapted for use in the present computer-based

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systems. As used herein, a "target sequence" can be any nucleic acid or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. The most preferred sequence length of a target sequence is from about 10 to 300 amino acids, more preferably from about 30 to 100 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures and inducible expression elements (protein binding sequences).

3.12 TRIPLE HELIX FORMATION

In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA or RNA, both of which methods are based on the binding of a polynucleotide sequence to DNA or RNA. Polynucleotides suitable for use in these methods are preferably 20 to 40 bases in length and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Olmno, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide.

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3.13 DIAGNOSTIC ASSAYS AND KITS

The present invention further provides methods to identify the presence or expression of one of the ORFs of the present invention, or homolog thereof, in a test sample, using a nucleic acid probe or antibodies of the present invention, optionally conjugated or otherwise associated with a suitable label.

In general, methods for detecting a polynucleotide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polynucleotide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polynucleotide of the invention is detected in the sample. Such methods can also comprise contacting a sample under stringent hybridization conditions with nucleic acid primers that anneal to a polynucleotide of the invention under such conditions, and amplifying annealed polynucleotides, so that if a polynucleotide is amplified, a polynucleotide of the invention is detected in the sample.

In general, methods for detecting a polypeptide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polypeptide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polypeptide of the invention is detected in the sample.

In detail, such methods comprise incubating a test sample with one or more of the antibodies or one or more of the nucleic acid probes of the present invention and assaying for binding of the nucleic acid probes or antibodies to components within the test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of immunoassays:

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Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

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3.14 MEDICAL IMAGING

The novel polypeptides and binding partners of the invention are useful in medical imaging of sites expressing the molecules of the invention (e.g., where the polypeptide of the invention is involved in the immune response, for imaging sites of inflammation or infection). See, e.g., Kunkel et al., U.S. Pat. NO. 5,413,778. Such methods involve chemical attachment of a labeling or imaging agent, administration of the labeled polypeptide to a subject in a pharmaceutically acceptable carrier, and imaging the labeled polypeptide *in vivo* at the target site.

3.15 SCREENING ASSAYS

Using the isolated proteins and polynucleotides of the invention, the present invention further provides methods of obtaining and identifying agents which bind to a polypeptide encoded by an ORF corresponding to any of the nucleotide sequences set forth in SEQ ID NOs: 1 - 362, or bind to a specific domain of the polypeptide encoded by the nucleic acid. In detail, said method comprises the steps of:

- (a) contacting an agent with an isolated protein encoded by an ORF of the present invention, or nucleic acid of the invention; and
 - (b) determining whether the agent binds to said protein or said nucleic acid.

In general, therefore, such methods for identifying compounds that bind to a polynucleotide of the invention can comprise contacting a compound with a polynucleotide of the invention for a time sufficient to form a polynucleotide/compound complex, and detecting the complex, so that if a polynucleotide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Likewise, in general, therefore, such methods for identifying compounds that bind to a polypeptide of the invention can comprise contacting a compound with a polypeptide of the invention for a time sufficient to form a polypeptide/compound complex, and detecting the complex, so that if a polypeptide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Methods for identifying compounds that bind to a polypeptide of the invention can also comprise contacting a compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives

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expression of a receptor gene sequence in the cell, and detecting the complex by detecting reporter gene sequence expression, so that if a polypeptide/compound complex is detected, a compound that binds a polypeptide of the invention is identified.

Compounds identified via such methods can include compounds which modulate the activity of a polypeptide of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds which modulate the expression of a polynucleotide of the invention (that is, increase or decrease expression relative to expression levels observed in the absence of the compound). Compounds, such as compounds identified via the methods of the invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

The agents screened in the above assay can be, but are not limited to, peptides, carbohydrates, vitamin derivatives, or other pharmaceutical agents. The agents can be selected and screened at random or rationally selected or designed using protein modeling techniques.

For random screening, agents such as peptides, carbohydrates, pharmaceutical agents and the like are selected at random and are assayed for their ability to bind to the protein encoded by the ORF of the present invention. Alternatively, agents may be rationally selected or designed. As used herein, an agent is said to be "rationally selected or designed" when the agent is chosen based on the configuration of the particular protein. For example, one skilled in the art can readily adapt currently available procedures to generate peptides, pharmaceutical agents and the like, capable of binding to a specific peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: Antisense Peptides," In Synthetic Peptides, A User's Guide, W.H. Freeman, NY (1992), pp. 289-307, and Kaspczak et al., Biochemistry 28:9230-8 (1989), or pharmaceutical agents, or the like.

In addition to the foregoing, one class of agents of the present invention, as broadly described, can be used to control gene expression through binding to one of the ORFs or EMFs of the present invention. As described above, such agents can be randomly screened or rationally designed/selected. Targeting the ORF or EMF allows a

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skilled artisan to design sequence specific or element specific agents, modulating the expression of either a single ORF or multiple ORFs which rely on the same EMF for expression control. One class of DNA binding agents are agents which contain base residues which hybridize or form a triple helix formation by binding to DNA or RNA. Such agents can be based on the classic phosphodiester, ribonucleic acid backbone, or can be a variety of sulfhydryl or polymeric derivatives which have base attachment capacity.

Agents suitable for use in these methods preferably contain 20 to 40 bases and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide and other DNA binding agents.

Agents which bind to a protein encoded by one of the ORFs of the present invention can be used as a diagnostic agent. Agents which bind to a protein encoded by one of the ORFs of the present invention can be formulated using known techniques to generate a pharmaceutical composition.

3.16 USE OF NUCLEIC ACIDS AS PROBES

Another aspect of the subject invention is to provide for polypeptide-specific nucleic acid hybridization probes capable of hybridizing with naturally occurring nucleotide sequences. The hybridization probes of the subject invention may be derived from any of the nucleotide sequences SEQ ID NOs: 1 - 362. Because the corresponding gene is only expressed in a limited number of tissues, a hybridization probe derived from of any of the nucleotide sequences SEQ ID NOs: 1 - 362 can be used as an indicator of the presence of RNA of cell type of such a tissue in a sample.

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Any suitable hybridization technique can be employed, such as, for example, in situ hybridization. PCR as described in US Patents Nos. 4,683,195 and 4,965,188 provides additional uses for oligonucleotides based upon the nucleotide sequences. Such probes used in PCR may be of recombinant origin, may be chemically synthesized, or a mixture of both. The probe will comprise a discrete nucleotide sequence for the detection of identical sequences or a degenerate pool of possible sequences for identification of closely related genomic sequences.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA polymerase and the appropriate radioactively labeled nucleotides. The nucleotide sequences may be used to construct hybridization probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well known genetic and/or chromosomal mapping techniques. These techniques include in situ hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to known chromosomes, and the like. The technique of fluorescent in situ hybridization of chromosome spreads has been described, among other places, in Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York NY.

Fluorescent *in situ* hybridization of chromosomal preparations and other physical chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found in the 1994 Genome Issue of Science (265:1981f). Correlation between the location of a nucleic acid on a physical chromosomal map and a specific disease (or predisposition to a specific disease) may help delimit the region of DNA associated with that genetic disease. The nucleotide sequences of the subject invention may be used to detect differences in gene sequences between normal, carrier or affected individuals.

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3.17 PREPARATION OF SUPPORT BOUND OLIGONUCLEOTIDES

Oligonucleotides, i.e., small nucleic acid segments, may be readily prepared by, for example, directly synthesizing the oligonucleotide by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer.

Support bound oligonucleotides may be prepared by any of the methods known to those of skill in the art using any suitable support such as glass, polystyrene or Teflon. One strategy is to precisely spot oligonucleotides synthesized by standard synthesizers. Immobilization can be achieved using passive adsorption (Inouye & Hondo, (1990) J. Clin. Microbiol. 28(6) 1469-72); using UV light (Nagata *et al.*, 1985; Dahlen *et al.*, 1987; Morrissey & Collins, (1989) Mol. Cell Probes 3(2) 189-207) or by covalent binding of base modified DNA (Keller *et al.*, 1988; 1989); all references being specifically incorporated herein.

Another strategy that may be employed is the use of the strong biotin-streptavidin interaction as a linker. For example, Broude *et al.* (1994) Proc. Natl. Acad. Sci. USA 91(8) 3072-6, describe the use of biotinylated probes, although these are duplex probes, that are immobilized on streptavidin-coated magnetic beads. Streptavidin-coated beads may be purchased from Dynal, Oslo. Of course, this same linking chemistry is applicable to coating any surface with streptavidin. Biotinylated probes may be purchased from various sources, such as, e.g., Operon Technologies (Alameda, CA).

Nunc Laboratories (Naperville, IL) is also selling suitable material that could be used. Nunc Laboratories have developed a method by which DNA can be covalently bound to the microwell surface termed Covalink NH. CovaLink NH is a polystyrene surface grafted with secondary amino groups (>NH) that serve as bridge-heads for further covalent coupling. CovaLink Modules may be purchased from Nunc Laboratories. DNA molecules may be bound to CovaLink exclusively at the 5'-end by a phosphoramidate bond, allowing immobilization of more than 1 pmol of DNA (Rasmussen *et al.*, (1991) Anal. Biochem. 198(1) 138-42).

The use of CovaLink NH strips for covalent binding of DNA molecules at the 5'-end has been described (Rasmussen et al., (1991). In this technology, a phosphoramidate bond is employed (Chu et al., (1983) Nucleic Acids Res. 11(8) 6513-29). This is beneficial as immobilization using only a single covalent bond is preferred. The phosphoramidate bond

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joins the DNA to the CovaLink NH secondary amino groups that are positioned at the end of spacer arms covalently grafted onto the polystyrene surface through a 2 nm long spacer arm. To link an oligonucleotide to CovaLink NH via an phosphoramidate bond, the oligonucleotide terminus must have a 5'-end phosphate group. It is, perhaps, even possible for biotin to be covalently bound to CovaLink and then streptavidin used to bind the probes.

More specifically, the linkage method includes dissolving DNA in water (7.5 ng/ul) and denaturing for 10 min. at 95°C and cooling on ice for 10 min. Ice-cold 0.1 M 1-methylimidazole, pH 7.0 (1-MeIm₇), is then added to a final concentration of 10 mM 1-MeIm₇. A ss DNA solution is then dispensed into CovaLink NH strips (75 ul/well) standing on ice.

Carbodiimide 0.2 M 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), dissolved in 10 mM 1-MeIm₇, is made fresh and 25 ul added per well. The strips are incubated for 5 hours at 50°C. After incubation the strips are washed using, e.g., Nunc-Immuno Wash; first the wells are washed 3 times, then they are soaked with washing solution for 5 min., and finally they are washed 3 times (where in the washing solution is 0.4 N NaOH, 0.25% SDS heated to 50°C).

It is contemplated that a further suitable method for use with the present invention is that described in PCT Patent Application WO 90/03382 (Southern & Maskos), incorporated herein by reference. This method of preparing an oligonucleotide bound to a support involves attaching a nucleoside 3'-reagent through the phosphate group by a covalent phosphodiester link to aliphatic hydroxyl groups carried by the support. The oligonucleotide is then synthesized on the supported nucleoside and protecting groups removed from the synthetic oligonucleotide chain under standard conditions that do not cleave the oligonucleotide from the support. Suitable reagents include nucleoside phosphoramidite and nucleoside hydrogen phosphorate.

An on-chip strategy for the preparation of DNA probe for the preparation of DNA probe arrays may be employed. For example, addressable laser-activated photodeprotection may be employed in the chemical synthesis of oligonucleotides directly on a glass surface, as described by Fodor *et al.* (1991) Science 251(4995) 767-73, incorporated herein by reference. Probes may also be immobilized on nylon supports as described by Van Ness *et al.* (1991) Nucleic Acids Res. 19(12) 3345-50; or linked to Teflon using the method of

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Duncan & Cavalier (1988) Anal. Biochem. 169(1) 104-8; all references being specifically incorporated herein.

To link an oligonucleotide to a nylon support, as described by Van Ness *et al.* (1991), requires activation of the nylon surface via alkylation and selective activation of the 5'-amine of oligonucleotides with cyanuric chloride.

One particular way to prepare support bound oligonucleotides is to utilize the light-generated synthesis described by Pease *et al.*, (1994) PNAS USA 91(11) 5022-6, incorporated herein by reference). These authors used current photolithographic techniques to generate arrays of immobilized oligonucleotide probes (DNA chips). These methods, in which light is used to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays, utilize photolabile 5'-protected *N*-acyl-deoxynucleoside phosphoramidites, surface linker chemistry and versatile combinatorial synthesis strategies. A matrix of 256 spatially defined oligonucleotide probes may be generated in this manner.

3.18 PREPARATION OF NUCLEIC ACID FRAGMENTS

The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or YAC inserts, and RNA, including mRNA without any amplification steps. For example, Sambrook *et al.* (1989) describes three protocols for the isolation of high molecular weight DNA from mammalian cells (p. 9.14-9.23).

DNA fragments may be prepared as clones in M13, plasmid or lambda vectors and/or prepared directly from genomic DNA or cDNA by PCR or other amplification methods. Samples may be prepared or dispensed in multiwell plates. About 100-1000 ng of DNA samples may be prepared in 2-500 ml of final volume.

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described at 9.24-9.28 of Sambrook *et al.* (1989), shearing by ultrasound and NaOH treatment.

Low pressure shearing is also appropriate, as described by Schriefer *et al.* (1990) Nucleic Acids Res. 18(24) 7455-6, incorporated herein by reference). In this method, DNA samples are passed through a small French pressure cell at a variety of low to intermediate pressures. A lever device allows controlled application of low to intermediate pressures to

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the cell. The results of these studies indicate that low-pressure shearing is a useful alternative to sonic and enzymatic DNA fragmentation methods.

One particularly suitable way for fragmenting DNA is contemplated to be that using the two base recognition endonuclease, $Cvi\Pi$, described by Fitzgerald *et al.* (1992) Nucleic Acids Res. 20(14) 3753-62. These authors described an approach for the rapid fragmentation and fractionation of DNA into particular sizes that they contemplated to be suitable for shotgun cloning and sequencing.

The restriction endonuclease *Cvi*JI normally cleaves the recognition sequence PuGCPy between the G and C to leave blunt ends. Atypical reaction conditions, which alter the specificity of this enzyme (*Cvi*JI**), yield a quasi-random distribution of DNA fragments form the small molecule pUC19 (2688 base pairs). Fitzgerald *et al.* (1992) quantitatively evaluated the randomness of this fragmentation strategy, using a *Cvi*JI** digest of pUC19 that was size fractionated by a rapid gel filtration method and directly ligated, without end repair, to a lac Z minus M13 cloning vector. Sequence analysis of 76 clones showed that *Cvi*JI** restricts pyGCPy and PuGCPu, in addition to PuGCPy sites, and that new sequence data is accumulated at a rate consistent with random fragmentation.

As reported in the literature, advantages of this approach compared to sonication and agarose gel fractionation include: smaller amounts of DNA are required (0.2-0.5 ug instead of 2-5 ug); and fewer steps are involved (no preligation, end repair, chemical extraction, or agarose gel electrophoresis and elution are needed

Irrespective of the manner in which the nucleic acid fragments are obtained or prepared, it is important to denature the DNA to give single stranded pieces available for hybridization. This is achieved by incubating the DNA solution for 2-5 minutes at 80-90°C. The solution is then cooled quickly to 2°C to prevent renaturation of the DNA fragments before they are contacted with the chip. Phosphate groups must also be removed from genomic DNA by methods known in the art.

3.19 PREPARATION OF DNA ARRAYS

Arrays may be prepared by spotting DNA samples on a support such as a nylon membrane. Spotting may be performed by using arrays of metal pins (the positions of which correspond to an array of wells in a microtiter plate) to repeated by transfer of about 20 nl of a DNA solution to a nylon membrane. By offset printing, a density of dots higher than the

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density of the wells is achieved. One to 25 dots may be accommodated in 1 mm², depending on the type of label used. By avoiding spotting in some preselected number of rows and columns, separate subsets (subarrays) may be formed. Samples in one subarray may be the same genomic segment of DNA (or the same gene) from different individuals, or may be different, overlapped genomic clones. Each of the subarrays may represent replica spotting of the same samples. In one example, a selected gene segment may be amplified from 64 patients. For each patient, the amplified gene segment may be in one 96-well plate (all 96 wells containing the same sample). A plate for each of the 64 patients is prepared. By using a 96-pin device, all samples may be spotted on one 8 x 12 cm membrane. Subarrays may contain 64 samples, one from each patient. Where the 96 subarrays are identical, the dot span may be 1 mm² and there may be a 1 mm space between subarrays.

Another approach is to use membranes or plates (available from NUNC, Naperville, Illinois) which may be partitioned by physical spacers e.g. a plastic grid molded over the membrane, the grid being similar to the sort of membrane applied to the bottom of multiwell plates, or hydrophobic strips. A fixed physical spacer is not preferred for imaging by exposure to flat phosphor-storage screens or x-ray films.

The present invention is illustrated in the following examples. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention. Accordingly, it is intended that the broader aspects of the present invention not be limited to the disclosure of the following examples. The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and compositions and methods which are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations which should be placed upon the scope of the invention are those which appear in the appended claims.

All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

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4.0 EXAMPLES

4.1 EXAMPLE 1

Novel Nucleic Acid Sequences Obtained From Various Libraries

A plurality of novel nucleic acids were obtained from cDNA libraries prepared from various human tissues and in some cases isolated from a genomic library derived from human chromosome using standard PCR, SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using primers specific for the vector sequences which flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (e.g., 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones were selected for sequencing.

In some cases, the 5' sequence of the amplified inserts was then deduced using a typical Sanger sequencing protocol. PCR products were purified and subjected to fluorescent dye terminator cycle sequencing. Single pass gel sequencing was done using a 377 Applied Biosystems (ABI) sequencer to obtain the novel nucleic acid sequences. In some cases RACE (Random Amplification of cDNA Ends) was performed to further extend the sequence in the 5' direction.

4.2 EXAMPLE 2

Novel Nucleic Acids

The novel nucleic acids of the present invention of the invention were assembled from sequences that were obtained from a cDNA library by methods described in Example 1 above, and in some cases sequences obtained from one or more public databases. The nucleic acids were assembled using an EST sequence as a seed. Then a recursive algorithm was used to extend the seed EST into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 114, gb pri 114, and UniGene version 101) that belong to this assemblage. The algorithm terminated when there was no additional sequences from the above databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

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Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e., dbEST version 120, gb pri 120, UniGene version 120, Genepet release 120). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, ed-ext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide and amino acid sequences, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS: 1- 362.

Table 1 shows the various tissue sources of SEQ ID NO: 1-362.

The homology for SEQ ID NO: 1-362 were obtained by a BLASTP version 2.0al 19MP-WashU search against Genpept release 120 and the amino acid version of Geneseq released on October 26, 2000, using BLAST algorithm. The results showed homologues for SEQ ID NO: 1-362 from Genpept. The homologues with identifiable functions for SEQ ID NO: 1-362 are shown in Table 2 below.

Using eMatrix software package (Stanford University, Stanford, CA) (Wu et al., J. Comp. Biol., Vol. 6 pp. 219-235 (1999) herein incorporated by reference), all the sequences were examined to determine whether they had identifiable signature regions. Table 3 shows the signature region found in the indicated polypeptide sequences, the description of the signature, the eMatrix p-value(s) and the position(s) of the signature within the polypeptide sequence.

Using the pFam software program (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1) pp. 320-322 (1998) herein incorporated by reference) all the polypeptide sequences were examined for domains with homology to certain peptide domains. Table 4 shows the name of the domain found, the description, the p-value and the pFam score for the identified domain within the sequence.

The nucleotide sequence within the sequences that codes for signal peptide sequences and their cleavage sites can be determine from using Neural Network SignalP V1.1 program (from Center for Biological Sequence Analysis, The Technical University of Denmark). The process for identifying prokaryotic and eukaryotic signal peptides and their cleavage sites are also disclosed by Henrik Nielson, Jacob Engelbrecht, Soren

Brunak, and Gunnar von Heijne in the publication "Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites" Protein Engineering, Vol. 10, no. 1, pp. 1-6 (1997), incorporated herein by reference. A maximum S score and a mean S score, as described in the Nielson et as reference, was obtained for the polypeptide sequences. Table 5 shows the position of the signal peptide in each of the polypeptides and the maximum score and mean score associated with that signal peptide.

TABLE 1

TISSUE ORIGIN	LIBRARY/	HYSEQ LIBRARY	SEQ ID NOS:
	RNA SOURCE	NAME	oly it noo.
adult brain	GIBCO	AB3001	4 18 39-40 83 88 98 110 112-
			113 136 168-169 201-203
adult brain	GIBCO	ABD003	7 15-16 31-32 39-41 45 54 58
			63 70 73-75 82-84 92 98 106
			110 114 116-117 126 128 130
			139 144 155 164 168-169 191-
			192 195 198 204-215 239-240
	01 1	TDD001	249 252 258 272-274
adult brain	Clontech	ABR001	10-11 15 19 39-40 88 106 120
adult brain	Clantach	7.DD006	144 168 215-216 258
adult brain	Clontech	ABR006	13 17 20 23 33 39-40 50 58 62
			75 82 84 88 100 104 121-122
			129 149 168 208 216 223 232-
			233 239 256 269 277 287-288
adult brain	Clontech	ABR008	353 360 4 10-11 13 17 20 23 25 28-30
addic Diain	CTOHCECH	סטאמא	32 34-35 39-41 48 50 53-54 58
			61 63 68-69 74 76 78 80 84-89
			91 98 104 107 112-114 118 121-
			122 130 134-136 143 153-155
			158-160 163-166 168 172-173
			184-188 199-200 203 212-213
			215-216 219-220 226-227 234
			239 242 244 251-252 255-257
			263 268 271-272 277-280 287
			291 300-301 305-306 316 322
			338 346-347 360
adult brain	Clontech	ABR011	157 306
adult brain	BioChain	ABR012	36 247
adult brain	Invitrogen	ABR013	176
adult brain	Invitrogen	ABR014	50 53 100 269
adult brain	Invitrogen	ABR015	19 38 74 161-162
brain	Invitrogen	ABR016	53 74 137 139 239
adult brain	Invitrogen	ABT004	8 15 19-20 28 30 35 75 78 100
			106-107 113 134 160 179 181
			184 198-199 210 216 224 227
adinogutas	C+ xo+ o zono	70001	252 254-255 288 340
adipocytes	Stratagene	ADP001	9 13 19 45 74 98 121-122 131 164 187 189-190 217 239
adrenal gland	Clontech	ADR002	9 15 18-19 24-25 31-32 46 56
aurenar Arana	CTOHCECH	WALLOUS	77-78 112 114-115 117-119 121-
			122 124 139 170 182 192 209
			213 218 220 225 249 276 306
adult heart	GIBCO	AHR001	2 4 7 17 19-22 26-27 34 38 45-
	01200	11111001	46 50 53-54 58 60-61 63 74 76-
			77 86-87 91 96 98 108 112 114
			121-122 131 133 136-140 144
			155 160 165-168 184 188 217
			226 239 241-242 251 259 265
			277-278 290 306
adult kidney	GIBCO	AKD001	4 6-11 13 15-17 19-20 24 30-32

	/	LINGTO TERRIBU	SEQ ID NOS:
TISSUE ORIGIN	LIBRARY/	HYSEQ LIBRARY	SEQ ID NOS:
	RNA SOURCE	NAME	24 26 20 47 52 54 60 62 66 60
			34 36-38 47 53-54 60-63 66 69
			73-75 78 82-85 87 89-92 96 98
			100 103 106 108 110 112-113
			116 121-123 126 129 131 134
			136 139-142 144 153 155 158-
			159 169-170 176 181 207 237
			239 266-267 271-272 306
adult kidney	Invitrogen	AKT002	7-8 10-11 13 15 19 25-27 32
addit kidney	Inviciogen	11111002	37-38 53 55-56 66 75 86 90 92
			108 123 144 165-166 172 182
			199 218 225 233 236 238 260
			266-267 332
adult lung	GIBCO	ALG001	8 22 26-28 38-40 47 54 78 91
			98 104 110 112 117 139 148 168
			189 196 225 239 248 351-352
lymph node	Clontech	ALN001	7 26-27 32 35 38-40 79 82 120
			127 152 158-159 169 171 219
			239 244
	GIBCO	ALV001	7 14 16-17 19 33 37 53 72 77
young liver	GIBCO	ALVOOT	107 113 116 118 134 152 168
			1
			212 249
adult liver	Invitrogen	ALV002	12 14 17 24 28 32-33 36 58 73
			75-76 84 101 116 131 138 140
			158-160 182 194 212 238 275
			284 323 342-343
adult liver	Clontech	ALV003	271 284 358
ovary	Invitrogen	AOV001	4 6-11 13 15-16 18-21 25-27
Ovary	1111122109011	110.00	31-32 34 36 38-40 46 48 50 53-
			54 56 58 60 65 70 73-78 80 83-
			84 86 91-92 95 98 100-101 103-
			106 108 110-112 115 117-118
			124 126-127 129-131 136 139-
			142 144 148 155 157-161 163-
			167 169 173-174 178 180-186
			188-189 191-193 196 199-200
			204-208 210-211 220-223 233
			236 239 249-252 260-263 266-
			270 287-288 306 315 351-352
placenta	Clontech	APL001	30 50 74 82 230
	Invitrogen	APL002	45 50 59 70 75 103 163 223
placenta		ASP001	7 19 30 38 45 54 58 62 74 81
adult spleen	GIBCO	ASPUUL	83 91 106 110 112-113 116 131
			144 151 155 162 165-166 172
			176 189 191 215 230 236 239
			249 329
testis	GIBCO	ATS001	4 15 19-20 30 48 53 74 89 94
			110 126 140 158-159 173 214-
			215 220 239 245 306
bladder	Invitrogen	BLD001	30 35 59 61 74-75 123 164 221
pradder	THATCTOGET	770001	241 318
	03 1 3	DMD001	3 6-7 9 13 17 20 26-27 30-31
bone marrow	Clontech	BMD001	34 38-40 42 46 53-54 63-79 82-
			83 85 91 93-98 101 105 110 115
1		1	121-122 126 128-129 133-134

mrggir opicin	LIBRARY/	HYSEQ LIBRARY	SEQ ID NOS:
TISSUE ORIGIN	RNA SOURCE	NAME	DIQ 10 NOO!
	KNA SOUNCE	TAT 71 1173	143 145 154 161-162 176 192
			205-206 234 236 239 243 264
			289 306 322
bone marrow	Clontech	BMD002	3-4 7 9 13 16-17 19-20 23 30
DOILC MALLOW	0101100011		32 34 36 38-40 47-48 54-56 58
			61 68-69 74-75 79 84 108 118-
			119 121-122 125 128-129 131
			133 140 144 147 149 153-154
			158-159 161 163 167 171 174
			176 185-187 200 211 218 232
			239 241 247 252 277-278 285
			296 303 310 320 324 329 339
			341 353 356 359
bone marrow	Clontech	BMD004	64
colon	Invitrogen	CLN001	18 32 100 106 110 143 153 163-
			164 178 213 247 266-267 284
cervix	BioChain	CVX001	4 6 8-9 19 22 24-25 28 32 45-
			46 53 55-56 63 74-75 77-78 83
			87 91-92 95 102 105 108 110 123 127 136-137 140 169 172
			182 184-186 189-191 199 211
			238 249 266-267 274 283 306-
	3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4		308 317 354
1 1 1 7 7	Chustagana	EDT001	2 4 6-7 9 15 17-21 25-28 30 32
endothelial	Stratagene	FDIOOI	36 39-40 45 47-48 53 55-57 60
cells			62-63 69-70 74-76 78 83 85-87
			98 101-104 106 108 112-113 119
			121-123 130-131 136-137 139-
			142 155-156 158-159 161 174
			189-192 204 208 218 220 223
			230 239 251 280 306
Genomic clones	Genomic	EPM001	223
from short arm	Data from		
of chromosome	Genetic		
8	Research		
Genomic clones	Genomic	EPM003	223
from short arm	Data from		
of chromosome	Genetic		
8	Research	EDV(0.0.4	222
Genomic clones	Genomic	EPM004	223
from short arm	Data from		
of chromosome	Genetic Research		
8	Clontech	FBR001	32 227
fetal brain fetal brain	Clontech	FBR004	319
fetal brain	Clontech	FBR004	7 10-11 13 17 20 23-25 28-29
Tecar Diain	0101100011		32 35 41-42 48 50 53 63 75 80
			89 91 104 112 121-122 125 130
			154 163 165-166 168 171 173
			191 199 210 215-216 218 226
			232 239 256 272 277 290 300
			306 309 319-320 333 353 360
fetal brain	Invitrogen	FBT002	15 17 19 35 69 75 87 104 109
			140 163 174 192-193 198-199

TISSUE ORIGIN	LIBRARY/	HYSEQ LIBRARY	SEQ ID NOS:
110000 0111011	RNA SOURCE	NAME	
			207 220 228 239 252 256-258
fetal heart	Invitrogen	FHR001	3 8 19 32 41 48 77-79 91 114
			119 126 163 165-166 172 174
			176 200 218 232 244 263 331
			351-352 360-361
fetal kidney	Clontech	FKD001	16-17 36 46 53 74 82 95 104
			111 117 169 189
fetal kidney	Clontech	FKD002	26-27 165-166 218 220 232 238 263 306
fetal kidney	Invitrogen	FKD007	38 74
fetal lung	Clontech	FLG001	32 48 139 173 217
fetal lung	Invitrogen	FLG003	10-11 19 36 58 61 69 74 134
			163 168 178 194 249 263 266-
			267 351-352
fetal liver-	Columbia	FLS001	1-19 21-38 41-62 68 70 72 74-
spleen	University		78 87 90-91 93 100-104 106-121
=			123-125 127 130-131 133-134
	,		141-142 144 149 155-156 161
			163 165-167 169 176 194-196
			200 207 210 221 224-225 227 231-233 236 238 263 303 306
			l l
		FT 7000	313 324 336 342 2 5 7-9 12 14 16-18 22-24 30-
fetal liver-	Columbia	FLS002	33 35-40 43-46 48-50 52-53 57
spleen	University		70 72 76-78 84-85 87 90 92
			101-102 106-108 110 112 114
			116-120 124 127-128 130-131
			134-135 140-142 144 155 163
			172 174 187 189-190 192 195-
			196 199 205-207 210 220-221
			223-224 230-234 244 251 258
			260-261 263 265 275 296 313-
			315 331 337-338 345 362
fetal liver-	Columbia	FLS003	19 30 33 139 174 265 313 339
spleen	University		355
fetal liver	Invitrogen	FLV001	10-11 14 17 19 21 37 46 50 61
			63 156 163 165-166 172 200 210
	<u> </u>		238 253
fetal liver	Clontech	FLV002	19 32 74 163 356
fetal liver	Clontech	FLV004	3 14 19 32-33 37 42 47-48 50
			58 60 82 85 121-122 129 131
			152 171 193 272 353
fetal muscle	Invitrogen	FMS001	28 32 39-40 45 48 50 57 74 107
			121-122 131 137 139-140 147
			173 204 230 281
fetal muscle	Invitrogen	FMS002	19 23 32 34 55-56 80-81 98
			121-122 124 131-132 158-159
			199 212 230 280-281 353 357
		DOMO 01	360 2 4 14-15 17-19 22 41 46 50 53
fetal skin	Invitrogen	FSK001	59 72 75-76 81-82 84 94 103
			106 113 128 135 140 144 156
			164 167 170 174 188 209-210
			220 227 230 238-239 254 306
	1		220 221 230 230 233 201 300

TISSUE ORIGIN	LIBRARY/ RNA SOURCE	HYSEQ LIBRARY NAME	SEQ ID NOS:
	TRIVIT DOGRAM		321-322 333-335
fetal skin	Invitrogen	FSK002	4 34 47 54 79 84 113 126-127 129 134 156 192-193 208 223 230 241 277 285 333
fetal spleen	BioChain	FSP001	32 104
umbilical cord	BioChain	FUC001	4 19 22-23 32 38-40 46 55-56 58 61 73-75 91 98-99 103 106 110 112 116 120 123 129-130 139 160 165-166 175 182 230 234 249 251 302
fetal brain	GIBCO	HFB001	6 9 16 19-20 25 32 35-36 39-41 45 48 53-54 56 60 73 80-81 83-92 98 107 112 114 157-159 163 165-166 172 191 197-198 211 226-227 239 350
infant brain	Columbia University	IB2002	6-8 13 15-17 19 21 32 35 41-42 48 50 60-61 77 81 84-85 88 92 104-106 112-113 116 119 134 139 144 160 165-166 168-169 173 176 191 196 199-201 215 223 225 227-228 239 261 285 290 329 339-340 348
infant brain	Columbia University	IB2003	7-9 13 32 39-41 58 92 103 105- 106 144 160 162 199 205-206 219 227-228 271 357
infant brain	Columbia University	IBM002	32 88 340
infant brain	Columbia University	IBS001	6 26-27 32 164 199 340
lung, fibroblast	Stratagene	LFB001	2 4 18-19 25 39-40 46 53 55-56 106 112 124 129 136 139 146 150 164 169 189-190 215 230 239 260 349
adult lung	Invitrogen	LGT002	2 6 8-11 15-16 19 26-28 30 32 39-40 46 48 50 53-56 60-61 66 72 74-75 85 87 92 94 96 98 103-104 108 110 112-113 117 119-120 124 130-131 139-140 149 152-153 155 158-159 167 169 174 176 178 184 189-190 195-196 217 220 229-230 234- 239 248-250 263 265-267 280 286 310 329-330 351-352
lymphocyte	ATCC	LPC001	7 13 16 19 32 39-40 54 63 74 82 96 113 120 126 130-131 133 144 150 178 184-186 223 239 241 260 262 294 305 339
leukocytes	GIBCO	LUC001	1 3-4 7-9 13 16-20 26-27 30 32 34-35 38-40 46 48 51 53-56 63 66 70 72-76 78 82 84-85 87 89 91-92 95-96 101 106 108 110- 112 114 116 120-122 126-127 129-133 136 139 144 146-152 164 175-179 187 192 232 236

TISSUE ORIGIN	LIBRARY/	HYSEQ LIBRARY	SEQ ID NOS:
1	RNA SOURCE	NAME	_
			239 241 266-267 292-294 306
			325-327 329 339 359
leukocytes	Clontech	LUC003	7-8 17 55-56 76 84 112 129 131 161-162 176 180 185-186 329
melanoma	Clontech	MEL004	4 13 17 28 30-31 39-40 83 85
	,		92 113 126 129 139 160 162 182
			198 232 239 303 324
mammary gland	Invitrogen	MMG001	8-11 16-21 28 30 32 35 41 45
			58-59 61 72 74-75 78 84 87 92
	}		103-104 106-107 110 113 115- 116 123 128 131 134-135 144
			152 163 176 181 183 210 212
			220-221 230 234 236 238-239
			248 251 260 272-273 275-276
			306 331 351-352 360
neuron	Stratagene	NTD001	18-19 39-40 45 74 78 85 91
neuron	Stratagene	NTR001	19 21 57 246 265
neuronal cells	Stratagene	NTU001	8-9 18-19 21 32 81 85 87 128
nituitore.	Clontech	DITO 0 4	164 174 184 13 47 82 87 98 112 288 354
pituitary gland		PIT004	
placenta	Clontech	PLA003	13 48 50 58 77 100 106 112 126
	07 1	DD#001	129 152 178 232
prostate	Clontech	PRT001	16 19 22 26-27 32 34 46-47 76- 77 92 98 106 112 124 172 214
			239 260 280 294
rectum	Invitrogen	REC001	8 10-11 18 30 54 74-76 106 113
			123-124 143 163 172 213 220
			232 237 260 322-323 340
salivary gland	Clontech	SAL001	8 19 36 74 83 104 118 124 150
21-2-	7 ECC	GEDOO3	176 260 295 304 239
skin fibroblast	ATCC	SFB002	239
small	Clontech	SIN001	9 17 19 22 32 34 54 57 59-60
intestine	:		73 75 84-85 96 99 107 113 118
			134 139 144 149 151 185-187
			189 197 199 217 219 221 230-
			231 248 250 253-254 260 266- 267 295 304 356
skeletal	Clontech	SKM001	17 19 39-40 48 89 104 116 131
muscle			281
spinal cord	Clontech	SPC001	8 19 32 34 38-40 47 58 61 74
-			80 83-84 89 104 108 131 139-
			140 168 187 213 226 236 239
			300 350
adult spleen	Clontech	SPLc01	1 46 54 134 236
stomach	Clontech	ST0001	7 32 38-40 51 66 74 76 89 117 124 128 169 229 239 253 280
			124 128 169 229 239 253 280 294 296
thalamus	Clontech	THA002	24 30 50 87 124 127 143 163
cnazamas	OTOILCEOIL		201 207 220 223 230 266-267
			269 279
thymus	Clontech	THM001	7 13 19 25 32 36 39-40 54-56
			72 74 82 96 108 113 119 127

TISSUE ORIGIN	LIBRARY/ RNA SOURCE	HYSEQ LIBRARY NAME	SEQ ID NOS:
			137 139 141-142 146 169 184 192 260 276 296
thymus	Clontech	THMc02	9 17 28 30 32 39-40 48 53 61 72 74-75 77 79 82 91 107 112 119-122 125-126 131 139-142 153 171 175-176 178 184 187 205-206 222-223 227 235-236 269 278 289 297 305 310-311 325 327-329 336
thyroid gland	Clontech	THR001	7-11 15 17 19-20 25-27 32 34 36 46 48 53 59 72 82-87 89 91 96 98-99 104 106 110 118-119 121-122 127 130 136 139 144 151-152 158-159 165-167 179 187 204 208 220 239 249 281 283 295 298-299 312 316 344
trachea	Clontech	TRC001	62-63 73 75 86-87 89 101 147 192 239 266-267 282-283
uterus	Clontech	UTR001	4 8 17 19 22 26-27 32 39-40 46 63 82 98 110 130 151

TABLE 2

SEQ ID	ACCESSION	DESCRIPTION	SMITH-	ાં
NO:	NUMBER		WATERMAN	IDENTITY
			SCORE	
1	L29075	Dictyostelium discoideum G-box	173	21
		binding factor		
2	AL359215	Streptomyces coelicolor A3(2)	133	28
		putative phosphoglycerate mutase.		
3	AF228713	Homo sapiens EDAG-1	1671	100
4	AC007130	Homo sapiens similar to 3-	1557	100
		hydroxyisobutyrate dehydrogenase;		1
		similar to P29266 (PID:g416873)		
5	AB040926	Homo sapiens KIAA1493 protein	1973	98
6	AF193016	Homo sapiens methyltransferase COQ3	1609	99
7	U95825	Homo sapiens androgen-induced	2968	63
•		prostate proliferative shutoff		
		associated protein		
8	AL390081	Homo sapiens SEMA4B, Semaphorin 4B	3560	99
9	AC002130	Arabidopsis thaliana F1N21.9	258	50
10	Z38061	Saccharomyces cerevisiae mal5,	323	27
10	230001	stal, len: 1367, CAI: 0.3,		
		AMYH YEAST P08640 GLUCOAMYLASE S1		
		(EC 3.2.1.3)		
11	D88733	Equine herpesvirus 1 membrane	284	24
_ T	100,00	glycoprotein		
13	M80783	Homo sapiens B12 protein	1144	70
14	U72678	Mus musculus EF-9	792	92
15	AK026486	Homo sapiens unnamed protein	427	83
		product		
16	AK025813	Homo sapiens unnamed protein	1010	100
		product		
17	AF151036	Homo sapiens HSPC202	722	84
18	AY007148	Homo sapiens similar to Homo	984	100
		sapiens HSPC197 mRNA with GenBank		
		Accession Number AF151031.1		
19	X57432	Rattus rattus ribosomal protein S2	956	97
20	AF164793	Homo sapiens protein x 013	386	100
21	J02642	Homo sapiens glyceraldehyde 3-	1639	95
- -		phosphate dehydrogenase (EC		
		1.2.1.12)		
22	M34573	Homo sapiens alpha-2 collagen type	515	100
2.2	1.010.0	VI-a		
23	AL109928	Homo sapiens dJ551D2.5 (novel	1999	100
20	112203320	protein)		
24	AF111858	Homo sapiens dimethylglycine	3918	99
23	1111111000	dehydrogenase precursor		
25	U64854	Caenorhabditis elegans partial CDS	184	25
26	AF151072	Homo sapiens HSPC238	838	99
27	AF151072	Homo sapiens HSPC238	393	96
28	AK024825	Homo sapiens unnamed protein	1794	99
۷0	ALOSAOS	product		
			+	175
20	AF285631	Rattus norwegicus secretory carrier	1 894	1 13
29	AF285631	Rattus norvegicus secretory carrier membrane protein 4	894	75

SEQ ID NO:	ACCESSION NUMBER	DESCRIPTION	SMITH- WATERMAN SCORE	% IDENTITY
		product		
31	AL161515	Arabidopsis thaliana putative protein	146	52
32	AJ007798	Homo sapiens stromal antigen 3, (STAG3)	6320	99
33	D31856	Bacillus subtilis Hutl protein, imidazolone-5-propionate hydrolase	667	39
34	AL391145	Arabidopsis thaliana putative protein	423	24
35	AF134726	Homo sapiens G7A	1591	46
36	AJ276485	Homo sapiens integral membrane transporter protein	1502	100
37	J05158	Homo sapiens carboxypeptidase N (EC 3.4.17.3)	2274	88
38	X57351	Homo sapiens 1-8D	673	97
39	AF230904	Homo sapiens c-Cbl-interacting protein	3437	100
40	AF230904	Homo sapiens c-Cbl-interacting protein	2615	99
41	AF276893	Homo sapiens p21-activated protein kinase 6	3550	100
42	AF269255	Homo sapiens lysosomal apyrase-like protein 1	3198	100
43	S85655	Homo sapiens prohibitin	742	84
44	AB040926	Homo sapiens KIAA1493 protein	1973	98
45	AF151063	Homo sapiens HSPC229	1012	100
46	X68277	Homo sapiens protein-tyrosine phosphatase	1886	100
47	Z98745	Homo sapiens dJ29K1.2	889	51
48	AF032668	Rattus norvegicus rsec15	3738	92
50	AF195534	Rattus norvegicus GERp95	4513	99
51	AF161368	Homo sapiens HSPC105	513	98
52	W73147	Amino acid sequence of the soluble complement receptor 1	651	81
53	AF271212	Homo sapiens disrupter of silencing SAS10	2431	100
54	AF116646	Homo sapiens PRO0082	598	100
55	AF145613	Drosophila melanogaster BcDNA.GH03108	817	46
56	AF145613	Drosophila melanogaster BcDNA.GH03108	884	38
57	AL023803	Homo sapiens dJ616B8.3 (novel gene)	2287	100
59	AC024877	Caenorhabditis elegans contains similarity to Pfam families PF00621 (Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases, score=58.2, E=1.7e-13, N=10 and PF00169 (PH (pleckstrin homology) domain, score=17.0, E=0.00071, N=1)	296	31
60	AL390114	Leishmania major probable proteophosphoglycan	154	30
61	AL031427	Homo sapiens dJ167A19.1 (novel	732	51

SEQ ID NO:	ACCESSION NUMBER	DESCRIPTION	SMITH- WATERMAN SCORE	
		protein)	BOOKE	
62	AL390935	Leishmania major possible CG17807 protein	151	43
63	J04067	Canis familiaris microsomal signal peptidase	930	99
64	AF062378	Mus musculus calmodulin-binding protein SHA1	1782	60
65	AE001002	Archaeoglobus fulgidus ATP- dependent RNA helicase, putative	195	29
66	X69065	Erythroid ankyrin [Mus musculus]	181	30
68	AF017807	Homo sapiens Arp2/3 complex 16kDa subunit	371	100
69	AC007660	Arabidopsis thaliana putative translation initiation factor	173	29
70	AJ243177	Xenopus laevis Xenopus RPA interacting protein alpha	447	42
71	AF226055	Homo sapiens HTGN29	1367	100
72	AF090930	Homo sapiens PRO0478	180	89
73	AF118084	Homo sapiens PRO1914	350	98
74	AB028893	Homo sapiens ribosomal protein S11	824	100
75	AK024500	Homo sapiens FLJ00109 protein	1514	100
76	AF238866	Mus musculus LNR42	1041	99
7 7	AC026875	Arabidopsis thaliana T6D22.6	129	30
78	U42436	Caenorhabditis elegans Hypothetical protein C49H3.3	130	32
79	M80902	Homo sapiens AHNAK nucleoprotein	8529	99
80	W90962	Human CSGP-2 protein [homo sapiens]	2346	99
81	AF206661	Gallus gallus neuronal tetraspanin	1066	81
82	S73591	Homo sapiens brain-expressed HHCPA78 homolog VDUP1	800	42
83	AF116650	Homo sapiens PRO0786	302	100
84	L26335	Cavia porcellus zinc finger protein	1493	99
85	AF209198	Homo sapiens zinc finger protein 277	2357	100
86	AE001399	Plasmodium falciparum GAF domain protein (cyclic nt signal transduct.)	178	35
87	Y48226	Human prostate cancer-associated protein 12 [Homo sapiens]	1204	96
88	M94389	Loligo pealei neurofilament protein	165	23
89	AF121775	Homo sapiens nasopharyngeal carcinoma susceptibility protein LZ16	903	58
90	AF116675	Homo sapiens PRO1942	257	100
91	AE002760	Drosophila melanogaster CG14464 gene product	195	43
92	AK000100	Homo sapiens unnamed protein product	841	100
93	AB020236	Homo sapiens ribosomal protein L27A	754	99
94	AF119865	Homo sapiens PRO2176	470	97
96	AF138863	Homo sapiens PRO1677	868	99
97	X14361	Homo sapiens CR-1 receptor SCR9 (or	135	100

SEQ ID NO:	ACCESSION NUMBER	DESCRIPTION	SMITH- WATERMAN SCORE	% IDENTITY
		16) C-term. (21 is 3rd base in codon) (106 is 1st base in codon)		
98	Z24725	Homo sapiens mitogen inducible gene mig-2	3576	99
99	U64598	Caenorhabditis elegans weakly similar to S. cervisiae PTM1 precursor (SP:P32857)	398	45
100	AC004770	Homo sapiens BC269730 4	1527	84
101	AL139075	Campylobacter jejuni NOL1\NOP2\sun family protein	312	35
102	AF113694	Homo sapiens PRO1359	416	100
103	U15158	Homo sapiens ESP-2	564	41
104	AL020996	Homo sapiens dJ317E23.3 (novel protein)	1818	99
105	AF161370	Homo sapiens HSPC107	824	100
106	AK000161	Homo sapiens unnamed protein product	284	100
107	AK001784	Homo sapiens unnamed protein product	684	100
108	AE000913	Methanobacterium thermoautotrophicum conserved protein	221	25
109	AF165527	Homo sapiens DGCR8	859	100
110	AF230200	Homo sapiens OVN6-2	358	95
111	Z72516	Caenorhabditis elegans T25G3.1	180	36
112	AF201940	Homo sapiens DC6	505	100
113	AK001301	Homo sapiens unnamed protein product	2040	98
114	U23515	Caenorhabditis elegans weakly similar to gastrula zinc finger protein	205	47
115	AF228021	Bos taurus cyclophilin I	345	91
116	AF166124	Homo sapiens selenoprotein X	527	100
117	AF079445	Dictyostelium discoideum TipC	529	30
118	AB032179	Homo sapiens similar to mouse Ehm2	2255	100
119	U89867	Homo sapiens nuclear matrix protein 55	2449	98
120	U29056	Mus musculus Src-like adapter protein	352	47
121	U22015	Mus musculus retinoid X receptor interacting protein	2190	73
122	AF113538	Homo sapiens retinoid x receptor interacting protein	1800	100
123	AK000158	Homo sapiens unnamed protein product	740	100
124	AF260924	Mus musculus UFD2/D4COLE1E fusion protein	1222	82
125	U12465	Homo sapiens ribosomal protein L35	591	97
126	AJ277591	Homo sapiens p15-2a protein	749	100
127	AF205599	Mus musculus transposase-like protein	2406	74
128	U58975	Homo sapiens proto-oncogene	659	90

SEQ ID NO:	ACCESSION NUMBER	DESCRIPTION	SMITH- WATERMAN SCORE	% IDENTITY
129	X98374	Rattus norvegicus KIS	2193	99
130	AF151049	Homo sapiens HSPC215	627	100
131	M59807	Homo sapiens putative	907	99
132	U12979	Homo sapiens PC4	563	99
133	AF076642	Homo sapiens regulator of G-protein	1218	100
		signaling 13		
134	AF116718	Homo sapiens PRO2900	396	100
135	AC018758	Homo sapiens GPI-anchored metastasis-associated protein homolog	213	31
136	AC025416	Arabidopsis thaliana F5011.12	135	36
137	M83186	Homo sapiens cytochrome c oxidase subunit VIIa	247	100
138	AF232937	Mus musculus thymic stroma derived lymphopoietin	247	41
139	M15841	Homo sapiens U2 small nuclear ribonucleoprotein B''	638	100
140	AK026916	Homo sapiens unnamed protein product	2612	99
141	Y05317	<pre>Human secreted protein bn97_1 [Homo sapiens]</pre>	1508	100
142	Y05317	<pre>Human secreted protein bn97_1 [Homo sapiens]</pre>	851	99
143	AF041083	Rattus norvegicus RoBo-1	139	25
144	AC024260	Arabidopsis thaliana cell division control protein, putative; 15914-18846	194	25
146	AL022398	Homo sapiens dJ434014.3.2 (putative protein) (isoform 2)	575	100
147	AF212842	Homo sapiens immunoglobulin-like transcript 11 protein	1280	99
148	AB042827	Rattus norvegicus Nadrin	477	66
149	AK001841	Homo sapiens unnamed protein product	1916	100
150	AJ278120	Homo sapiens putative ankyrin- repeat containing protein	540	98
151	AL135959	Homo sapiens dJ233G16.1 (novel protein)	770	100
152	Y58196	[Homo sapiens] Human STRAP-3 protein, encoded by testis EST AI139607	671	100
153	U41060	Homo sapiens LIV-1 protein	373	50
154	AJ007590	Homo sapiens XRP2 protein	1766	100
155	AB046868	Xenopus laevis beta-catenin- interacting protein	125	46
156	AB027258	Homo sapiens basal transcriptional activator hABT1	1408	100
157	AF039656	Homo sapiens neuronal tissue- enriched acidic protein	1109	96
158	AK001425	Homo sapiens unnamed protein product	1695	99
159	AK001425	Homo sapiens unnamed protein	858	98

SEQ ID	ACCESSION	DESCRIPTION	SMITH-	%
NO:	NUMBER		WATERMAN	IDENTITY
			SCORE	
1.00	7.770.000.000	product	1000	100
160	AK002030	Homo sapiens unnamed protein product	1029	100
161	X79417	Sus scrofa 40S ribosomal protein S12	510	83
162	X12597	Homo sapiens HMG-1 protein (AA 1-215)	1140	99
163	AK001159	Homo sapiens unnamed protein product	764	100
164	AK000020	Homo sapiens unnamed protein product	1613	100
165	AK001322	Homo sapiens unnamed protein product	1207	100
166	AK001322	Homo sapiens unnamed protein product	892	98
167	AE003822	Drosophila melanogaster CG8493 gene product	357	36
168	AF023451	Bos taurus guanine nucleotide- exchange protein	187	21
169	AK000154	Homo sapiens unnamed protein - product	673	100
170	AJ132702	Mus musculus ATFa-associated factor	435	64
172	AL022311	Homo sapiens dJ1014D13.3 (novel	405	38
		protein)		
174	AB017634	Mus musculus ENP	770	65
175	U40407	synthetic construct T cell receptor alpha chain	1119	80
176	AF043179	Homo sapiens T cell receptor beta chain	681	73
177	AF116678	Homo sapiens PRO1995	587	100
178	AF217522	Homo sapiens uncharacterized bone marrow protein BM046	262	42
179	AB046074	Macaca fascicularis unnamed protein product	515	83
180	X79417	Sus scrofa 40S ribosomal protein S12	429	84
181	AF002668	Homo sapiens MLD	1235	65
182	AB036422	Bos taurus molybdopterin cofactor sulfurase	3509	79
184	AF036696	Caenorhabditis elegans contains similarity to Brassica oleracea non-green plastid phosphate/triose- phosphate translocator precursor (GB:U13632)	662	42
185	AJ277276	Homo sapiens rapa-2	5155	99
186	AJ277275	Homo sapiens rapa-1	5086	100
187	U22296	Rattus norvegicus casein kinase 1 gamma 1 isoform	1444	93
188	AE003750	Drosophila melanogaster CG9996 gene product	468	44
189	Z97056	Homo sapiens dJ434P1.2 (KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum	1103	100

SEQ ID NO:	ACCESSION NUMBER	DESCRIPTION	SMITH- WATERMAN	% IDENTITY
			SCORE	
190	AF081126	protein retention receptor 3) Drosophila melanogaster ER lumen	409	75
192	AF226047	protein retaining receptor Homo sapiens GL002	863	100
193	AF269167	Homo sapiens arsenite related gene	906	60
193	AF 209107	1	906	00
195	U41805	Mus musculus putative T1/ST2 receptor binding protein precursor	162	26
197	AL357374	Homo sapiens bA353C18.2 (novel protein)	404	97
199	M34551	Homo sapiens 52-kD Ro/SSA ribonucleoprotein	964	42
202	AF230201	Homo sapiens OVC10-2	396	100
203	AK001984	Homo sapiens unnamed protein product	658	100
204	AK000530	Homo sapiens unnamed protein product	691	100
205	U37134	Drosophila melanogaster inturned protein	248	23
206	U37134	Drosophila melanogaster inturned protein	244	23
208	AB033130	Mus musculus testis-specific gene	871	85
209	AK000464	Homo sapiens unnamed protein product	221	100
210	AJ277557	Homo sapiens mitochondrial 5'(3')- deoxyribonucleotidase (dNT-2)	617	100
211	AF127564	Arabidopsis thaliana ubiquitin- protein ligase 1	854	42
213	Y17108	Homo sapiens rhomboid-related protein	485	39
214	AL132776	Homo sapiens dJ393D12.2 (novel LIM domain protein)	1660	99
215	U73819	Mus musculus polypeptide GalNAc transferase-T4	1039	42
216	AL035406	Homo sapiens dJ233K16.1 (KIAA0444, 3844 a putative chromodomain helicase DNA binding protein 3 (CHD3))		100
217	M15800	Homo sapiens MAL protein	308	42
218	L29554	Rattus norvegicus alpha 2,6- 942 sialyltransferase		80
219	AL137315	Homo sapiens hypothetical protein	983	100
220	AK026027	Homo sapiens unnamed protein product	647	100
221	AL137584	Homo sapiens hypothetical protein	246	97
223	AC005498	Homo sapiens R31665_1	1752	78
225	AC010155	Arabidopsis thaliana F3M18.5	171	34
226	AL080276	Homo sapiens dJ101K10.2 (regulator of G-protein signaling 17 (RGS17) (RGSZ2))	1126	100
227	AF042345	Homo sapiens truncated EVI5	1815	64
228	J04214	Bos taurus retinaldehyde-binding protein precursor	504	39

SEQ ID	ACCESSION	DESCRIPTION	SMITH-	8
NO:	NUMBER		WATERMAN SCORE	IDENTITY
230	AF181263	Homo sapiens EH domain containing 2	2816	99
231	AP001660	Homo sapiens putative gene, multidrug resistance associated protein like	1424	100
232	AB000910	Sus scrofa ribosomal protein	542	100
233	AL133404	Homo sapiens dJ238023.9 (novel protein similar to rat SAC (soluble adenylyl cyclase))	298	100
234	X51397	Mus musculus MyD88 protein (AA 1-243)	136	25
235	X01403	Homo sapiens T-cell receptor alpha- chain	840	90
236	X14254	Rattus rattus invariant chain (AA 1-280)	745	77
238	U23084	Saccharomyces cerevisiae Ynl0470p	344	35
239	X03342	Homo sapiens rpL32 (aa 1-135)	152	96
240	AF116669	Homo sapiens PRO1828	237	100
241	U23181	Caenorhabditis elegans final exon in repeat region; similar to long tandem repeat region of sialidase (SP:TCNA_TRYCR, P23253) and neurofilament H protein	135	25
242	AF263913	Mus musculus fidgetin	3864	97
243	AF090892	Homo sapiens PRO0106	290	100
244	U21310	Caenorhabditis elegans F40H6.3 gene product	153	27
246	AK001673	Homo sapiens unnamed protein product	3661	100
247	AL022603	Arabidopsis thaliana putative protein	166	43
248	AL023803	Homo sapiens dJ616B8.3 (novel gene)	339	42
249	X52140	Rattus norvegicus precursor polypeptide (AA -28 to 1152)	5429	87
250	AB020755	Arabidopsis thaliana gene id:MZN1.18~unknown protein	139	46
251	AE003619	Drosophila melanogaster CG7224 gene product	186	43
252	AC004997	Homo sapiens match to ESTs Z43979 (NID:g573097), R19699 (NID:g774333), and C01164 (NID:g1433394); alternatively spliced form of H_DJ130H16.1a (Cterminal truncation confirmed by C01164)	388	67
254	AE003588	Drosophila melanogaster CG13947 gene product	115	42
256	Y50934	Human fetal brain cDNA clone vc30_1 498 derived protein #1 [Homo sapiens]		100
257	AF242768	Homo sapiens mesenchymal stem cell protein DSC43	1554	100
259	м95779	Bos taurus G protein gamma-5 subunit	333	98

	NUMBER AL035521 F247501	Arabidopsis thaliana putative	WATERMAN SCORE	IDENTITY
		Arabidopsis thaliana putative		1
261 A	F247501	protein	145	28
		Drosophila melanogaster PINEAPPLE EYE	333	36
	L034548	Homo sapiens dJ1103G7.2 (novel protein)	262	100
	F119851	Homo sapiens PRO1722	143	63
	41834	Ensis minor nuclear protein	173	26
	97966	Homo sapiens calcyphosine	963	100
267 X	97966	Homo sapiens calcyphosine	660	95
269 A	F022383	Homo sapiens complexin I	668	99
271 Y	10054	Rattus norvegicus 3-hydroxy-3- methylglutaryl CoA lyase	224	67
274 Al	F153201	Homo sapiens zinc finger protein dp	179	36
275 X8	85738	Bos taurus novel brain-specific protein	326	55
277 Al	F250342	Arabidopsis thaliana SMC-related protein MSS2	266	39
278 AI	L080242	Homo sapiens bA554C12.1 (RBX1 or ROC1 (ring-box or ring finger protein 1))	131	100
279 Z8	83760	Ciona intestinalis COS41.4	1162	62
	41534	Caenorhabditis elegans similar to yeast MAK16 protein (SP:MK16 YEAST, P10962)	721	54
281 A	F272975	Gallus gallus smoothelin-C	543	37
	L035414	Homo sapiens dJ667H12.2.2 (novel protein (isoform 2))	588	100
283 AE	F116661	Homo sapiens PRO1438	145	62
	K001757	Homo sapiens unnamed protein product	1300	100
287 U2	20897	Homo sapiens melanoma ubiquitous mutated protein	2133	100
289 UC	09847	Homo sapiens zinc finger protein	880	100
290 A.	J000079	Trypanosoma cruzi glycosylphosphatidylinositol- specific phospholipase C	225	26
	F156549	Mus musculus putative E1-E2 ATPase	2108	49
	F161345	Homo sapiens HSPC082	439	100
294 AF	F116694	Homo sapiens PRO2219	351	88
295 M7	74027	Homo sapiens mucin	461	39
298 AI	L133640	Homo sapiens hypothetical protein	2149	100
299 M1	L7886	Homo sapiens acidic ribosomal phosphoprotein (P1)	161	76
300 Y9	99368	Human PRO1326 (UNQ686) amino acid sequence SEQ ID NO:100 [Homo sapiens]	300	32
303 AE	003708	Drosophila melanogaster CG6171 gene product	144	27
304 M3	32639	Homo sapiens statherin precursor	276	87
305 Z8	33844	Homo sapiens dJ37E16.2 (SH3-domain binding protein 1)	897	96

SEQ ID	ACCESSION	DESCRIPTION	SMITH-	96
NO:	NUMBER		WATERMAN	IDENTITY
			SCORE	
306	AE003791	Drosophila melanogaster CG18065	120	32
		gene product		
307	AF135026	Homo sapiens kallikrein-like	1392	100
210	7 7 1 0 0 0 5 7	protein 3 splice variant 1		
310	AF198257	Felis catus immunoglobulin kappa	678	76
211	7.577.05	light chain		
311	X57725	Homo sapiens TCR Vbeta 22a	626	100
312	AC018513	Homo sapiens unknown	818	100
313	X03249	Bos taurus epsilon-4 beta-globin	321	79
314	AB046099	Macaca fascicularis unnamed protein product	395	88
315	AC006033	Homo sapiens T cell receptor gamma	1017	95
		chain; match to S08328		1
		(PID:g106470)		
316	AB046103	Macaca fascicularis unnamed protein	801	94
		product		
317	U88895	Homo sapiens ORF2	399	81
318	U09848	Homo sapiens zinc finger protein	242	49
319	AB003184	Homo sapiens ISLR	880	59
320	AB036921	Chrysophrys major maturation-	797	69
		inducing protein		
322	AF284422	Homo sapiens cation-chloride	4694	100
		cotransporter-interacting protein		
325	AE000659	Homo sapiens TCRAV8S2	577	100
327	R59748	T cell receptor Valpha2.3 chain	636	100
200	2 700 10 71	[homo sapiens]		
328	AJ004871	Homo sapiens TCR alpha chain	1328	94
329	AF043179	Homo sapiens T cell receptor beta chain	1286	92
330	AF090930	Homo sapiens PRO0478	140	50
332	AF077043	Homo sapiens 60S ribosomal protein L36	275	87
333	AL121988	Homo sapiens dJ34M23.3 (gap	1457	100
		junction protein, beta 4 (connexin		
		30.3))		
334	D86424	Mus musculus high-sulfur keratin	521	87
		protein]
335	AF090434	Fundulus heteroclitus cytochrome P450 2N1	760	40
336	AF116688	Homo sapiens PRO2133	370	98
337	X85372	Homo sapiens Sm protein F	222	84
338	D87009	Homo sapiens putative	1822	99
339	AE000860	Methanobacterium	631	35
		thermoautotrophicum conserved protein		
340	AL049759	Homo sapiens dJ930L11.1 (similar to KIAA0397)	1305	98
341	AE000004	Mycoplasma pneumonia MG207 homolog, 141 from M. genitalium		27
342	AF151076	Homo sapiens HSPC242	135	100
343	AB037902	Homo sapiens truncated aldo-keto	670	100
,	77001707	reductase	1010	100

SEQ ID NO:	ACCESSION NUMBER	DESCRIPTION	SMITH- WATERMAN SCORE	% IDENTITY
345	M33014	Drosophila melanogaster ubiquitin	153	62
346	AF053356	Homo sapiens leucin rich neuronal protein	580	46
348	AL137512	Homo sapiens hypothetical protein	751	100
349	S68015	Homo sapiens c6.1A	1664	100
350	AF151037	Homo sapiens HSPC203	318	100
351	AB036432	Homo sapiens advanced glycation endproducts receptor	2133	100
352	AB036432	Homo sapiens advanced glycation endproducts receptor	2094	96
353	AC006942	Homo sapiens R31181_2, partial protein	547	100
354	AF125535	Homo sapiens pp21 homolog	502	95
355	AF227130	Homo sapiens candidate taste receptor T2R3	1629	100
357	AB046626	Macaca fascicularis hypothetical protein	291	93
358	Z69597	Canis familiaris Rod transducin alpha subunit	1145	100
359	AE000659	Homo sapiens TCRAV16S1	565	100
360	Y99368	Human PRO1326 (UNQ686) Amino acid sequence SEQ ID NO:100. [Homo sapiens]	2034	100
362	L06499	Homo sapiens ribosomal protein L37a	187	55

TABLE 3

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
1	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR SIGNATURE	PR00651E 10.53 4.025e-06 60-80
2	BL00126	3'5'-cyclic nucleotide phosphodiesterases proteins.	BL00126B 15.20 7.750e-06 208-220
3	DM00892	3 RETROVIRAL PROTEINASE.	DM00892C 23.55 9.438e-07 285-319
4	BL00895	3-hydroxyisobutyrate dehydrogenase proteins.	BL00895B 21.14 7.061e-22 151-190 BL00895C 20.10 8.071e-22 200-236 BL00895A 12.61 1.973e-18 42-63
5	DM00099	4 kw A55R REDUCTASE TERMINAL DIHYDROPTERIDINE.	DM00099A 5.17 5.263e-06 409-415
7	PF00598	Influenza Matrix protein (M1).	PF00598C 19.35 3.333e-07 531-563
9	DM00522	499 kw TRYPSIN KINASE KUNITZ PANCREATIC.	DM00522A 8.30 3.250e-06 287-297
10	PR00514	5-HYDROXYTRYPTAMINE 1D RECEPTOR SIGNATURE	PR00514C 11.01 9.061e-07 81-100
11	PR00514	5-HYDROXYTRYPTAMINE 1D RECEPTOR SIGNATURE	PR00514C 11.01 9.061e-07 81-100
12	PR00775	90 KD HEAT SHOCK PROTEIN SIGNATURE	PR00775G 10.64 3.487e-07 8-27
13	PR00902	VP6 BLUE-TONGUE VIRUS INNER CAPSID PROTEIN SIGNATURE	PR00902K 11.09 1.000e-05 176-200
14	PR00875	MOLLUSC METALLOTHIONEIN SIGNATURE	PR00875A 5.83 1.127e-07 159-171 PR00875D 5.00 1.000e-05 158-169
15	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803C 7.00 9.200e-07 181-191 DM01803A 10.51 1.000e-06 178-199 DM01803C 7.00 7.337e-06 214-224
16	PF00803	3A movement protein.	PF00803D 14.15 2.622e-06 41-71
17	PR00170	SODIUM CHANNEL SIGNATURE	PR00170G 7.74 1.000e-05 24-53
18	PR00701	60KD INNER MEMBRANE PROTEIN SIGNATURE	PR00701E 13.83 5.684e-06 117-133
20	DM01415	6 SALIVARY GLUE PROTEIN.	DM01415A 6.65 6.063e-06 55-68
21	DM01418	352 FIBRILLAR COLLAGEN CARBOXYL- TERMINAL.	DM01418A 20.83 7.731e-06 64-112
22	BL00616	Histidine acid phosphatases phosphohistidine proteins.	BL00616D 15.83 7.268e-06 117-133

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
23	DM00611	9 kw LECTIN HTPG SERINE GNTR.	DM00611A 7.73 5.826e-06 173-181
24	BL00832	2'-5'-oligoadenylate synthetases proteins.	BL00832D 21.81 5.017e-06 425-449
25	PR00354	7FE FERREDOXIN SIGNATURE	PR00354C 5.72 8.590e-09 543-561
26	PR00217	43 KD POSTSYNAPTIC PROTEIN SIGNATURE	PR00217C 10.91 3.851e-07 89-105
27	PR00513	5-HYDROXYTRYPTAMINE 1B RECEPTOR SIGNATURE	PR00513A 7.75 1.439e-06 168-180
28	DM00552	GROWTH FACTOR AND CYTOKINES RECEPTORS FAMILY.	DM00552A 11.97 1.000e-05 130-152
29	PR00701	60KD INNER MEMBRANE PROTEIN SIGNATURE	PR00701I 8.59 3.088e-06 102-126
30	DM00060	338 kw NEUREXIN ALPHA III CYSTEINE.	DM00060 6.92 3.284e-07 680-690
34	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517D 7.66 6.971e-07 484-496
35	PR00701	60KD INNER MEMBRANE PROTEIN SIGNATURE	PR00701A 14.28 4.183e-06 722-744
37	PR00513	5-HYDROXYTRYPTAMINE 1B RECEPTOR SIGNATURE	PR00513C 10.79 8.927e-07 287-304
38	PR00166	AROMATIC AMINO ACID PERMEASE SIGNATURE	PR00166I 11.06 1.000e-05 98-118
39	PR00003	4-DISULPHIDE CORE SIGNATURE	PR00003A 14.69 3.803e-06 311-321
40	PR00003	4-DISULPHIDE CORE SIGNATURE	PR00003A 14.69 3.803e-06 311-321
41	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517D 7.66 8.788e-07 2-14
42	PR00701	60KD INNER MEMBRANE PROTEIN SIGNATURE	PR00701F 14.45 7.750e-06 25-46
43	DM00895	7 kw REVERSE TRANSCRIPTASE RNA POLYMERASE.	DM00895B 8.85 4.185e-06 157-167
44	DM00099	4 kw A55R REDUCTASE TERMINAL DIHYDROPTERIDINE.	DM00099A 5.17 5.263e-06 409-415
45	PR00519	5-HYDROXYTRYPTAMINE 5B RECEPTOR SIGNATURE	PR00519A 8.06 8.984e-06 137-154
46	PR00519	5-HYDROXYTRYPTAMINE 5B RECEPTOR SIGNATURE	PR00519B 9.99 1.828e-07 151-168
47	DM00892	3 RETROVIRAL PROTEINASE.	DM00892B 9.78 2.047e-06 21-27
48	BL00832	2'-5'-oligoadenylate synthetases	BL00832B 15.45 6.836e-07 375-416

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
		proteins.	
49	DM00588	8 kw CHO2 ALPHA ANTIGEN PARAMYOSIN.	DM00588A 10.87 7.128e-06 20-31
50	DM00604	2 SHIGA/RICIN RIBOSOMAL INACTIVATING TOXINS.	DM00604D 13.26 8.250e-06 263-273
51	BL01193	Ribosomal protein S8e proteins.	BL01193A 13.21 1.000e-05 19-50
52	PR00172	GLUCOSE TRANSPORTER SIGNATURE	PR00172F 8.47 9.901e-06 69-90
53	PR00297	10 KD CHAPERONIN SIGNATURE	PR00297A 13.91 4.740e-06 379-395
54	PR00320	G-PROTEIN BETA WD-40 REPEAT SIGNATURE	PR00320A 16.74 9.710e-06 81-96
55	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517C 5.36 4.126e-07 352-365
56	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517C 5.36 4.126e-07 352-365
57	DM00547	1 kw CHROMO BROMODOMAIN SHADOW GLOBAL.	DM00547E 13.94 4.656e-06 229-252
58	PF00506	Influenza virus nucleoprotein.	PF00506I 10.26 3.723e-06 32-68
60	DM00522	499 kw TRYPSIN KINASE KUNITZ PANCREATIC.	DM00522B 9.43 7.338e-07 171-185
61	DM01123	5 kw RESISTANCE TETRACYCLINE METHYLENOMYCIN EXPORT.	DM01123B 20.06 3.187e-06 205-244
62	PR00439	11-S SEED STORAGE PROTEIN FAMILY SIGNATURE	PR00439G 17.85 9.239e-07 82-100
63	PR00652	5-HYDROXYTRYPTAMINE 7 RECEPTOR SIGNATURE	PR00652F 11.66 4.767e-06 100-122
64	DM01785	72 PYRUVATE (FLAVODOXIN) DEHYDROGENASE.	DM01785A 14.90 2.196e-06 218-261
65	PR00652	5-HYDROXYTRYPTAMINE 7 RECEPTOR SIGNATURE	PR00652A 8.92 5.104e-06 315-336
67	BL00405	43 Kd postsynaptic protein.	BL00405F 8.07 9.920e-06 13-44
68	PR00380	KINESIN HEAVY CHAIN SIGNATURE	PR00380D 9.93 9.043e-06 44-66
69	PR00683	SPECTRIN PLECKSTRIN HOMOLOGY DOMAIN SIGNATURE	PR00683D 15.87 9.571e-06 46-65
70	PR00753	1-AMINOCYCLOPROPANE- 1-CARBOXYLATE SYNTHASE SIGNATURE	PR00753C 13.93 7.330e-06 192-213
71	PF00602	Influenza RNA- dependant RNA	PF00602J 9.52 9.727e-06 47-102

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
		polymerase subunit PB1.	
72	DM01855	PROTEIN-GLUTAMATE O- METHYLTRANSFERASE.	DM01855A 11.54 7.594e-06 27-44
74	BL01277	Ribonuclease PH proteins.	BL01277A 17.39 1.000e-05 50-88
75	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517G 16.45 6.919e-06 755-771
77	PF01073	3-beta hydroxysteriod dehydrogenase/isomer ase family.	PF01073B 12.26 9.767e-07 102-147
78	PR00351	MAS20 PROTEIN IMPORT RECEPTOR SIGNATURE	PR00351C 7.03 6.182e-06 99-112 PR00351C 7.03 1.000e-05 5-18
79	DM00611	9 kw LECTIN HTPG SERINE GNTR.	DM00611C 11.08 4.549e-06 1489- 1501
80	DM01111	4 kw PHOSPHATASE TRANSFORMING 61K PDF1.	DM01111C 9.35 2.800e-06 44-73
82	PD02407	3- BISPHOSPHOGLYCERATE- INDEPENDENT PHOSPHOGLYCER.	PD02407B 16.51 1.000e-06 94-111
83	PR00116	ARGINASE SIGNATURE	PR00116D 14.91 9.850e-06 14-44
84	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517F 11.48 7.250e-06 45-62
87	DM00522	499 kw TRYPSIN KINASE KUNITZ PANCREATIC.	DM00522B 9.43 3.535e-07 223-237
88	DM00303	6 LEA 11-MER REPEAT REPEAT.	DM00303A 13.20 8.034e-08 270-320
91	DM01242	3 THREONINETRNA LIGASE.	DM01242B 23.57 4.672e-06 71-120
92	PR00388	3',5'-CYCLIC NUCLEOTIDE CLASS II PHOSPHODIESTERASE SIGNATURE	PR00388E 6.66 3.797e-06 124-136
93	PD02407	3- BISPHOSPHOGLYCERATE- INDEPENDENT PHOSPHOGLYCER.	PD02407B 16.51 9.676e-06 15-32
94	PF00506	Influenza virus nucleoprotein.	PF00506I 10.26 4.555e-06 16-52
95	PR00551	2-S GLOBULIN FAMILY SIGNATURE	PR00551H 11.29 8.740e-06 21-39
96	PR00756	MEMBRANE ALANYL DIPEPTIDASE (M1) FAMILY SIGNATURE	PR00756E 11.91 9.338e-06 68-81
97	PR00547	X OPIOID RECEPTOR SIGNATURE	PR00547B 6.96 3.268e-06 17-36
98	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR	PR00651A 16.53 4.000e-06 653-674

SEQ ID NO:	ACCESSION	DESCRIPTION	RESULTS*
INO:	NO.	SIGNATURE	
99	PR00208	GLIADIN AND LMW GLUTENIN SUPERFAMILY SIGNATURE	PR00208C 11.51 9.775e-06 54-71
101	PR00451	CHITIN-BINDING DOMAIN SIGNATURE	PR00451A 6.49 1.000e-05 152-161
102	BL00832	2'-5'-oligoadenylate synthetases proteins.	BL00832B 15.45 7.569e-06 1-42
103	BL00405	43 Kd postsynaptic protein.	BL00405J 13.28 6.952e-06 142-176
104	DM01242	3 THREONINETRNA LIGASE.	DM01242F 10.61 5.500e-07 187-201
105	DM01834	8 HYDROGENASE (FE) SMALL CHAIN.	DM01834A 4.96 7.097e-06 53-60
107	PR00101	ASPARTATE CARBAMOYLTRANSFERASE SIGNATURE	PR00101E 5.52 1.000e-05 111-117
109	PR00902	VP6 BLUE-TONGUE VIRUS INNER CAPSID PROTEIN SIGNATURE	PR00902K 11.09 9.922e-06 91-115
110	PR00259	TRANSMEMBRANE FOUR FAMILY SIGNATURE	PR00259A 9.27 9.716e-06 9-33
111	BL00785	5'-nucleotidase proteins.	BL00785B 10.65 6.507e-06 53-67
112	PR00652	5-HYDROXYTRYPTAMINE 7 RECEPTOR SIGNATURE	PR00652G 10.94 5.429e-06 14-32
113	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517D 7.66 3.661e-06 372-384
114	PF00637	7-fold repeat proteins in Clathrin, also in VPS proteins.	PF00637D 7.09 9.449e-07 32-44
115	DM01235	5 kw T4 55.10 METHYLCYTOSINE TRANSCRIPTASE.	DM01235 20.29 9.832e-06 77-108
116	PR00873	ECHINOIDEA (SEA URCHIN) METALLOTHIONEIN SIGNATURE	PR00873C 6.16 9.906e-06 70-81
117	PR00387	3'5'-CYCLIC NUCLEOTIDE PHOSPHODIESTERASE SIGNATURE	PR00387D 10.81 4.889e-06 155-172
118	PF00598	Influenza Matrix protein (M1).	PF00598A 14.24 7.158e-06 211-254
119	BL00895	3-hydroxyisobutyrate dehydrogenase proteins.	BL00895B 21.14 8.036e-06 428-467
120	PR00419	ADRENODOXIN REDUCTASE FAMILY SIGNATURE	PR00419D 10.62 9.430e-06 18-33
121	DM00396	5 kw INTRON COI ND4L	DM00396B 7.85 3.739e-07 381-389

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
122	DI 00100	ND5.	
122	BL00198	4Fe-4S ferredoxins,	BL00198 10.43 5.500e-06 135-147
		iron-sulfur binding region proteins.	
123	DM01554	1 THYROLIBERIN	DM01554E 10.78 4.208e-06 93-110
	21101001	PRECURSOR.	DM01334E 10.78 4.208E-06 93-110
124	BL00405	43 Kd postsynaptic	BL00405G 7.78 6.294e-06 130-167
		protein.	
125	PR00298	60 KD CHAPERONIN	PR00298D 10.23 3.847e-06 14-40
		SIGNATURE	
126	PR00317	EPENDYMIN SIGNATURE	PR00317A 13.39 9.897e-06 79-99
127	PR00513	5-HYDROXYTRYPTAMINE	PR00513B 17.51 3.971e-06 277-290
		1B RECEPTOR	
130	PR00516	SIGNATURE 5-HYDROXYTRYPTAMINE	PRO05160 15 11 0 011 00 10
100	FROODIO	2A RECEPTOR	PR00516G 15.11 8.811e-06 18-35
		SIGNATURE	
131	PR00828	FORMIN SIGNATURE	PR00828F 8.56 1.000e-05 61-81
132	DM01269	303 kw ACTIVATING	DM01269A 23.35 7.279e-06 28-56
		RAN GTPASE ISOZYME.	2-10220311 23:33 7:2736 00 20 30
133	PR00586	PROSTANOID EP4	PR00586B 14.97 7.322e-06 10-28
		RECEPTOR SIGNATURE	PR00586H 8.65 9.791e-06 16-40
134	PF00954	S-locus glycoprotein	PF00954D 18.68 9.843e-06 9-44
105		family.	
135	PR00018	KRINGLE DOMAIN	PR00018A 14.52 1.000e-05 120-136
136	BL00115	SIGNATURE	
130	BF00112	Eukaryotic RNA polymerase II	BL00115E 14.13 9.921e-06 40-69
		heptapeptide repeat	
		proteins.	
137	PR00521	ANDROGEN RECEPTOR	PR00521A 17.02 9.729e-06 5-25
		SIGNATURE	
138	PR00701	60KD INNER MEMBRANE	PR00701I 8.59 5.267e-07 16-40
		PROTEIN SIGNATURE	
139	DM01269	303 kw ACTIVATING	DM01269A 23.35 7.085e-08 93-121
140	DD00015	RAN GTPASE ISOZYME.	
140	PR00915	LUTEOVIRUS GROUP 1 COAT PROTEIN	PR00915D 16.14 1.000e-05 374-392
		SIGNATURE	
143	DM00522	499 kw TRYPSIN	DM00522A 8.30 4.441e-06 94-104
	21100322	KINASE KUNITZ	DM00322A 0.30 4.441e-06 94-104
		PANCREATIC.	
144	PF00598	Influenza Matrix	PF00598B 13.10 1.623e-06 89-133
		protein (M1).	
145	PR00217	43 KD POSTSYNAPTIC	PR00217C 10.91 6.250e-06 24-40
1.5		PROTEIN SIGNATURE	
147	PR00701	60KD INNER MEMBRANE	PR00701A 14.28 6.049e-06 266-288
148	PR00513	PROTEIN SIGNATURE	DD00512D 11 06 0 000
T 4 0	EV00212	5-HYDROXYTRYPTAMINE 1B RECEPTOR	PR00513D 11.06 9.920e-06 103-121
		SIGNATURE	
149	PF00603	Influenza RNA-	PF00603D 8.49 9.319e-07 30-85
		dependant RNA	1100000D 0.43 3.3136-01 30-85
		polymerase subunit	

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.	DESCRIFTION	RESULTS*
		PA.	
150	DM01688	2 POLY-IG RECEPTOR.	DM01688N 11.93 9.920e-08 72-100
151	PF00637	7-fold repeat proteins in Clathrin, also in VPS proteins.	PF00637B 10.68 6.906e-06 186-195
152	BL00461	6-phosphogluconate dehydrogenase proteins.	BL00461A 15.90 1.764e-08 21-57
153	DM01554	1 THYROLIBERIN PRECURSOR.	DM01554A 6.07 2.565e-06 589-599
154	BL00405	43 Kd postsynaptic protein.	BL00405E 8.84 8.125e-06 109-135
155	PF00637	7-fold repeat proteins in Clathrin, also in VPS proteins.	PF00637A 15.49 5.179e-06 42-65
156	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517D 7.66 7.339e-06 85-97
157	DM01688	2 POLY-IG RECEPTOR.	DM01688P 13.54 1.925e-07 44-89 DM01688L 4.36 2.367e-07 123-133
159	PR00933	B-LYTIC METALLOENDOPEPTIDASE (M23) SIGNATURE	PR00933D 13.92 1.000e-05 85-106
161	PR00352	3FE-4S FERREDOXIN SIGNATURE	PR00352A 11.15 6.162e-06 94-106
163	BL00785	5'-nucleotidase proteins.	BL00785E 15.85 4.000e-06 95-111
164	PR00916	2C ENDOPEPTIDASE (C24) CYSTEINE PROTEASE FAMILY SIGNATURE	PR00916C 8.02 2.655e-06 121-133
165	BL00785	5'-nucleotidase proteins.	BL00785D 9.89 3.045e-06 154-164
166	BL00785	5'-nucleotidase proteins.	BL00785D 9.89 3.045e-06 123-133
167	DM01023	2 GLYCOSYL HYDROLASES FAMILY 5.	DM01023C 13.51 6.486e-06 149-175
168	PF00803	3A movement protein.	PF00803A 15.38 8.088e-06 255-290
169	PR00282	SNAKE CYTOTOXIN SIGNATURE	PR00282D 11.82 9.882e-06 74-85
170	PR00519	5-HYDROXYTRYPTAMINE 5B RECEPTOR SIGNATURE	PR00519B 9.99 5.787e-06 83-100
172	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803A 10.51 6.804e-06 136-157
173	PR00701	60KD INNER MEMBRANE PROTEIN SIGNATURE	PR00701E 13.83 9.724e-06 14-30
174	BL00118	Phospholipase A2 histidine proteins.	BL00118A 16.00 9.842e-06 132-145
175	DM01688	2 POLY-IG RECEPTOR.	DM01688G 16.45 1.825e-06 89-121
176	DM01930	2 kw FINGER SMCX SMCY YDR096W.	DM01930A 7.97 2.403e-07 146-159

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
177	PR00510	NEBULIN SIGNATURE	PR00510F 9.88 8.552e-06 34-51
179	PF00432	Prenyltransferase and squalene oxidase repeat proteins.	PF00432A 11.90 1.000e-05 27-39
180	PR00537	MU OPIOID RECEPTOR SIGNATURE	PR00537A 8.17 1.000e-05 27-41
183	PR00536	MELANOCYTE STIMULATING HORMONE RECEPTOR SIGNATURE	PR00536C 8.58 8.833e-06 64-82
184	DM00973	3 kw RESISTANCE BENOMYL YLL028W CYCLOHEXIMIDE.	DM00973B 17.81 8.261e-06 158-184
185	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517C 5.36 4.265e-06 718-731
186	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517C 5.36 4.265e-06 718-731
187	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR SIGNATURE	PR00651A 16.53 6.447e-06 144-165
188	BL01017	Ergosterol biosynthesis ERG4/ERG24 family proteins.	BL01017D 20.82 9.737e-06 21-67
191	DM00315	072 RIBONUCLEASE INHIBITOR.	DM00315B 6.84 7.459e-06 95-107
192	PR00930	HIGH MOBILITY GROUP PROTEIN (HMGY) SIGNATURE	PR00930E 5.98 9.740e-06 285-298
193	BL00794	7,8-dihydro-6- hydroxymethylpterin- pyrophosphokinase proteins.	BL00794B 22.12 8.967e-06 150-191
194	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517C 5.36 5.853e-06 115-128
196	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803A 10.51 7.031e-07 11-32
197	PR00171	SUGAR TRANSPORTER SIGNATURE	PR00171B 14.73 1.000e-05 15-35
198	PD02407	3- BISPHOSPHOGLYCERATE- INDEPENDENT PHOSPHOGLYCER.	PD02407J 10.55 6.610e-06 69-81
199	PF00604	Influenza RNA- dependant RNA polymerase subunit PB2.	PF00604F 10.21 2.417e-06 276-331
201	PR00409	PHTHALATE DIOXYGENASE REDUCTASE FAMILY SIGNATURE	PR00409D 13.02 9.900e-06 43-58
202	BL00660	Band 4.1 family	BL00660A 31.50 9.595e-06 1-54

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
		domain proteins.	
203	PR00745	GLYCOSYL HYDROLASE FAMILY 39 SIGNATURE	PR00745D 15.85 9.700e-06 68-83
204	PD01364	MUCIN GLYCOPROTEIN PRECURSOR MEM.	PD01364A 6.18 9.667e-06 9-16
205	BL00794	7,8-dihydro-6- hydroxymethylpterin- pyrophosphokinase proteins.	BL00794C 19.62 7.690e-07 309-347
206	BL00794	7,8-dihydro-6- hydroxymethylpterin- pyrophosphokinase proteins.	BL00794C 19.62 7.690e-07 309-347
207	DM00895	7 kw REVERSE TRANSCRIPTASE RNA POLYMERASE.	DM00895E 15.72 3.170e-06 241-266
208	PR00517	5-HYDROXYTRYPTAMINE 2C RECEPTOR SIGNATURE	PR00517D 7.66 4.835e-06 59-71
209	PD02365	CHAIN FACTOR INTERLEUKIN-12 BETA PRECURSOR IL-1.	PD02365C 7.89 9.719e-06 20-50
210	PR00551	2-S GLOBULIN FAMILY SIGNATURE	PR00551E 10.27 9.432e-06 19-34
211	DM01418	352 FIBRILLAR COLLAGEN CARBOXYL- TERMINAL.	DM01418B 22.51 3.289e-06 527-569
213	DM01785	72 PYRUVATE (FLAVODOXIN) DEHYDROGENASE.	DM01785E 12.98 6.400e-06 165-216
214	DM01834	8 HYDROGENASE (FE) SMALL CHAIN.	DM01834B 15.29 3.382e-06 64-90
215	PR00217	43 KD POSTSYNAPTIC PROTEIN SIGNATURE	PR00217C 10.91 4.583e-06 407-423
216	DM00547	1 kw CHROMO BROMODOMAIN SHADOW GLOBAL.	DM00547F 23.43 6.538e-36 628-675 DM00547E 13.94 2.400e-18 387-410 DM00547C 17.30 9.486e-16 266-288 DM00547B 11.28 9.217e-15 237-251 DM00547D 11.60 4.951e-12 357-371 DM00547A 12.38 6.455e-11 216-228
217	BL00407	Connexins proteins.	BL00407D 17.61 1.000e-05 57-87
218	BL00198	4Fe-4S ferredoxins, iron-sulfur binding region proteins.	BL00198 10.43 9.481e-06 74-86
219	DM01417	6 kw INDUCING XPMC2 MUSHROOM SPAC22G7.04.	DM01417B 15.47 3.550e-06 90-102
220	PR00519	5-HYDROXYTRYPTAMINE 5B RECEPTOR SIGNATURE	PR00519E 3.58 2.404e-07 184-199
221	PD01313	INTRON PROBABLE MATURASE CHLOROPLAST MR.	PD01313B 23.27 1.000e-05 10-45
222	PR00047	C4-TYPE STEROID	PR00047A 15.70 9.878e-06 99-116

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.	RECEPTOR ZINC FINGER	
		SIGNATURE	
223	DM01554	1 THYROLIBERIN PRECURSOR.	DM01554C 11.76 3.571e-06 255-271
224	DM01123	5 kw RESISTANCE TETRACYCLINE METHYLENOMYCIN EXPORT.	DM01123B 20.06 5.206e-06 28-67
226	BL00198	4Fe-4S ferredoxins, iron-sulfur binding region proteins.	BL00198 10.43 8.630e-07 28-40
227	BL00895	3-hydroxyisobutyrate dehydrogenase proteins.	BL00895B 21.14 5.173e-06 185-224
229	PR00907	THROMBOMODULIN SIGNATURE	PR00907G 11.63 9.794e-06 13-40
230	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR SIGNATURE	PR00651B 9.95 6.416e-06 62-77
231	DM00611	9 kw LECTIN HTPG SERINE GNTR.	DM00611C 11.08 9.113e-06 214-226
232	PR00582	PROSTANOID EP3 RECEPTOR SIGNATURE	PR00582B 9.74 1.000e-05 76-95
233	PR00407	EUKARYOTIC MOLYBDOPTERIN DOMAIN SIGNATURE	PR00407E 13.51 9.438e-06 176-192
234	DM00892	3 RETROVIRAL PROTEINASE.	DM00892C 23.55 9.913e-06 6-40
235	DM01688	2 POLY-IG RECEPTOR.	DM01688G 16.45 4.450e-06 94-126 DM01688J 14.69 6.000e-06 34-71
236	PD00930	PROTEIN GTPASE DOMAIN ACTIVATION.	PD00930A 25.62 1.000e-05 80-106
237	PR00076	6-PHOSPHOGLUCONATE DEHYDROGENASE SIGNATURE	PR00076B 11.24 6.418e-07 14-44
239	PR00243	MUSCARINIC ACETYLCHOLINE RECEPTOR SIGNATURE	PR00243F 16.45 9.182e-06 7-18
240	BL00854	Proteasome B-type subunits proteins.	BL00854B 10.97 1.000e-05 1-9
241	PR00513	5-HYDROXYTRYPTAMINE 1B RECEPTOR SIGNATURE	PR00513B 17.51 5.263e-07 876-889
242	DM01111	4 kw PHOSPHATASE TRANSFORMING 61K PDF1.	DM01111I 15.32 2.473e-07 522-552
243	BL00415	Synapsins proteins.	BL00415B 9.91 9.778e-06 53-89
244	BL00514	Fibrinogen beta and gamma chains C-terminal domain proteins.	BL00514E 14.28 1.000e-05 221-238
245	PR00187	ARTHROPOD HAEMOCYANIN SIGNATURE	PR00187B 15.70 1.000e-05 37-55

SEQ ID	ACCESSION NO.	DESCRIPTION	RESULTS*
246	PF00637	7-fold repeat proteins in Clathrin, also in VPS proteins.	PF00637C 27.33 1.184e-06 368-415
247	BL00785	5'-nucleotidase proteins.	BL00785A 9.73 7.557e-06 57-68
248	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR SIGNATURE	PR00651D 12.56 2.615e-06 228-249
249	PR00516	5-HYDROXYTRYPTAMINE 2A RECEPTOR SIGNATURE	PR00516B 10.78 1.811e-06 310-325
250	BL00461	6-phosphogluconate dehydrogenase proteins.	BL00461C 18.34 9.495e-06 30-58
251	BL00888	Cyclic nucleotide- binding domain proteins.	BL00888A 18.03 9.667e-06 20-37
252	DM01242	3 THREONINETRNA LIGASE.	DM01242E 23.00 6.215e-07 119-161
253	DM00250	kw ANNEXIN ANTIGEN PROLINE TUMOR.	DM00250A 10.52 6.488e-06 16-32
254	BL00291	Prion protein.	BL00291A 4.49 2.469e-07 51-86 BL00291A 4.49 6.878e-07 40-75 BL00291A 4.49 5.330e-06 22-57 BL00291A 4.49 1.000e-05 30-65
255	PF00506	Influenza virus nucleoprotein.	PF00506F 9.40 5.459e-08 17-55
256	BL00126	3'5'-cyclic nucleotide phosphodiesterases proteins.	BL00126A 27.56 6.026e-06 25-62
257	PR00003	4-DISULPHIDE CORE SIGNATURE	PR00003D 8.10 5.131e-06 291-300
258	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803C 7.00 7.061e-06 10-20
259	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803C 7.00 8.071e-06 3-13
260	PR00775	90 KD HEAT SHOCK PROTEIN SIGNATURE	PR00775D 8.91 3.831e-06 147-165
261	PR00217	43 KD POSTSYNAPTIC PROTEIN SIGNATURE	PR00217C 10.91 1.167e-06 75-91
262	PR00388	3',5'-CYCLIC NUCLEOTIDE CLASS II PHOSPHODIESTERASE SIGNATURE	PR00388D 14.87 8.079e-06 69-83
263	PR00023	ZONA PELLUCIDA SPERM-BINDING PROTEIN SIGNATURE	PR00023A 17.17 9.036e-06 24-39
264	BL00024	Hemopexin domain proteins.	BL00024F 11.30 9.894e-06 3-24
265	DM00303	6 LEA 11-MER REPEAT REPEAT.	DM00303A 13.20 6.294e-06 177-227
266	PR00652	5-HYDROXYTRYPTAMINE	PR00652A 8.92 9.224e-07 69-90

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
		7 RECEPTOR SIGNATURE	
267	PR00652 .	5-HYDROXYTRYPTAMINE 7 RECEPTOR SIGNATURE	PR00652A 8.92 9.224e-07 69-90
268	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803A 10.51 1.673e-06 14-35
270	PR00875	MOLLUSC METALLOTHIONEIN SIGNATURE	PR00875C 8.64 9.550e-06 65-77
271	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803A 10.51 7.308e-06 21-42
272	PF00598	Influenza Matrix protein (M1).	PF00598A 14.24 4.383e-06 46-89
273	PR00113	ALKALINE PHOSPHATASE SIGNATURE	PR00113D 6.87 9.260e-06 8-19
274	PD01841	PHOSPHORYLASE KINASE ALPHA MUSCL.	PD01841E 18.60 9.446e-06 80-118
275	PF00600	Influenza non- structural protein (NS1).	PF00600A 20.40 1.563e-06 40-67
276	PR00877	PLANT PEC FAMILY METALLOTHIONEIN SIGNATURE	PR00877B 4.74 9.878e-06 31-38
277	PR00076	6-PHOSPHOGLUCONATE DEHYDROGENASE SIGNATURE	PR00076E 12.73 6.417e-06 71-99
279	BL00101	Hexapeptide-repeat containing-transferases proteins.	BL00101A 10.95 1.000e-05 71-78
280	DM01111	4 kw PHOSPHATASE TRANSFORMING 61K PDF1.	DM01111M 10.67 2.629e-06 163-187
282	PR00049	WILM'S TUMOUR PROTEIN SIGNATURE	PR00049D 0.00 9.934e-06 35-50
283	PR00519	5-HYDROXYTRYPTAMINE 5B RECEPTOR SIGNATURE	PR00519C 9.73 1.227e-06 22-37
284	PR00304	TAILLESS COMPLEX POLYPEPTIDE 1 (CHAPERONE) SIGNATURE	PR00304E 7.79 1.000e-05 54-67
285	BL00197	2Fe-2S ferredoxins, iron-sulfur binding region proteins.	BL00197A 18.23 9.866e-07 49-79
286	PR00753	1-AMINOCYCLOPROPANE- 1-CARBOXYLATE SYNTHASE SIGNATURE	PR00753D 6.85 8.636e-06 61-83
287	PR00003	4-DISULPHIDE CORE SIGNATURE	PR00003B 7.64 1.300e-06 166-174
288	BL00940	Gamma-thionins family proteins.	BL00940A 20.51 9.671e-06 16-40
289	PD00066	PROTEIN ZINC-FINGER METAL-BINDI.	PD00066 13.92 9.609e-11 122-135 PD00066 13.92 1.900e-09 94-107 PD00066 13.92 2.703e-07 66-79

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
			PD00066 13.92 1.000e-05 38-51
291	PR00516	5-HYDROXYTRYPTAMINE 2A RECEPTOR SIGNATURE	PR00516F 10.18 9.609e-07 761-779
293	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR SIGNATURE	PR00651E 10.53 8.487e-06 51-71
296	PR00635	AT1 ANGIOTENSIN II RECEPTOR SIGNATURE	PR00635C 7.44 8.602e-06 28-45
297	PF00915	Calicivirus coat protein.	PF00915E 5.71 1.000e-05 102-112
298	PR00519	5-HYDROXYTRYPTAMINE 5B RECEPTOR SIGNATURE	PR00519B 9.99 3.968e-06 495-512
299	PR00784	MITOCHONDRIAL BROWN FAT UNCOUPLING PROTEIN SIGNATURE	PR00784D 15.86 9.730e-06 22-40
300	DM00973	3 kw RESISTANCE BENOMYL YLL028W CYCLOHEXIMIDE.	DM00973A 21.17 1.273e-06 7-44
301	PR00049	WILM'S TUMOUR PROTEIN SIGNATURE	PR00049D 0.00 8.752e-06 42-57
302	BL00283	Soybean trypsin inhibitor (Kunitz) protease inhibitors family.	BL00283B 16.55 1.000e-05 15-30
303	DM01753	6 kw OSTEOBLAST MAJOR IMMUNOGENIC MPB70.	DM01753A 21.93 9.830e-06 59-94
304	PR00516	5-HYDROXYTRYPTAMINE 2A RECEPTOR SIGNATURE	PR00516E 14.87 6.516e-06 20-38
305	DM01554	1 THYROLIBERIN PRECURSOR.	DM01554E 10.78 5.452e-07 20-37
306	PR00331	HAEMAGGLUTININ HA2 CHAIN SIGNATURE	PR00331E 18.67 1.000e-05 75-93
307	PR00651	5-HYDROXYTRYPTAMINE 2B RECEPTOR SIGNATURE	PR00651H 5.59 8.858e-06 152-175
308	BL00208	Plant hemoglobins proteins.	BL00208A 18.41 1.000e-05 5-47
309	PR00240	ALPHA-1A ADRENERGIC RECEPTOR SIGNATURE	PR00240E 9.25 9.391e-06 36-56
310	PR00701	60KD INNER MEMBRANE PROTEIN SIGNATURE	PR00701C 10.53 8.255e-06 55-76
311	PR00423	CELL DIVISION PROTEIN FTSZ SIGNATURE	PR00423B 7.15 1.000e-05 5-26
312	PF00602	Influenza RNA- dependant RNA polymerase subunit PB1.	PF00602C 12.16 2.068e-07 26-66
313	PR00246	SOMATOSTATIN RECEPTOR SIGNATURE	PR00246D 7.36 1.000e-05 4-14

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
314	BL00216	Sugar transport proteins.	BL00216A 13.29 9.526e-06 26-38
316	PF00721	Tobacco mosaic virus coat.	PF00721A 14.59 9.845e-06 131-167
317	PD00489	PROTEIN TRANSMEMBRANE TRANSPORT C.	PD00489A 15.57 1.000e-05 55-71
318	PR00163	RUBREDOXIN SIGNATURE	PR00163A 10.47 9.888e-06 59-76
319	PR00513	5-HYDROXYTRYPTAMINE 1B RECEPTOR SIGNATURE	PR00513A 7.75 9.149e-07 205-217
320	DM01418	352 FIBRILLAR COLLAGEN CARBOXYL- TERMINAL.	DM01418C 20.48 5.142e-06 377-419
321	BL00067	3-hydroxyacyl-CoA dehydrogenase proteins.	BL00067D 21.49 7.441e-06 9-42
322	DM01857	5 kw NUCLEOSIDE TRANSPORT DEPENDENT NA.	DM01857B 14.94 7.821e-08 52-80
323	DM01803	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803C 7.00 5.133e-06 43-53
324	PD01672	+ TRANSPORT EXCHANGER NA H TRANS.	PD01672B 15.16 1.000e-05 6-55
325	DM01688	2 POLY-IG RECEPTOR.	DM01688J 14.69 5.538e-06 31-68
327	DM00372	CARCINOEMBRYONIC ANTIGEN PRECURSOR AMINO-TERMINAL DOMAIN.	DM00372A 19.18 1.000e-05 9-54
328	DM01688	2 POLY-IG RECEPTOR.	DM01688J 14.69 4.308e-06 31-68
329	DM01930	2 kw FINGER SMCX SMCY YDR096W.	DM01930A 7.97 2.403e-07 144-157
330	PF00685	Sulfotransferase proteins.	PF00685A 19.12 9.370e-06 49-82
331	PR00347	PATHOGENESIS-RELATED PROTEIN SIGNATURE	PR00347A 13.98 9.649e-06 55-68
332	PR00538	MUSCARINIC M1 RECEPTOR SIGNATURE	PR00538F 10.59 8.667e-06 30-48
334	PR00159	2FE-2S FERREDOXIN SIGNATURE	PR00159A 9.58 1.153e-06 23-32
336	PR00554	ADENOSINE A2B RECEPTOR SIGNATURE	PR00554B 12.52 9.778e-06 41-50
337	DM01111	4 kw PHOSPHATASE TRANSFORMING 61K PDF1.	DM01111G 10.39 7.250e-06 3-44
338	PR00516	5-HYDROXYTRYPTAMINE 2A RECEPTOR SIGNATURE	PR00516B 10.78 7.649e-06 214-229
340	PR00388	3',5'-CYCLIC NUCLEOTIDE CLASS II PHOSPHODIESTERASE SIGNATURE	PR00388A 10.45 5.050e-06 141-160
342	DM01664	kw.	DM01664D 16.63 1.000e-05 22-47

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
343	PD01841	PHOSPHORYLASE KINASE ALPHA MUSCL.	PD01841K 14.81 1.000e-05 65-95
344	PR00416	EUKARYOTIC DNA TOPOISOMERASE I SIGNATURE	PR00416D 12.12 9.772e-06 23-40
345	BL00726	AP endonucleases family 1 proteins.	BL00726C 19.90 1.000e-05 7-33
346	BL00305	11-S plant seed storage proteins.	BL00305D 21.08 4.566e-06 465-507
347	PR00332	HISTIDINE TRIAD FAMILY SIGNATURE	PR00332A 10.15 9.890e-06 16-33
348	PR00518	5-HYDROXYTRYPTAMINE 5A RECEPTOR SIGNATURE	PR00518A 8.62 7.807e-06 19-36
349	BL00305	11-S plant seed storage proteins.	BL00305D 21.08 4.736e-06 276-318
350	PR00503	BROMODOMAIN SIGNATURE	PR00503C 19.84 9.731e-06 28-47
351	DM01688	2 POLY-IG RECEPTOR.	DM01688K 17.19 9.066e-07 81-120
352	DM01688	2 POLY-IG RECEPTOR.	DM01688K 17.19 9.066e-07 81-120
353	DM01415	6 SALIVARY GLUE PROTEIN.	DM01415B 13.78 5.273e-06 99-147
354	PR00216	OSTEOPONTIN SIGNATURE	PR00216F 11.79 9.913e-06 50-69
356	DM00895	7 kw REVERSE TRANSCRIPTASE RNA POLYMERASE.	DM00895G 3.62 9.913e-06 62-72
357	BL00126	3'5'-cyclic nucleotide phosphodiesterases proteins.	BL00126B 15.20 6.329e-06 35-47
358	PR00512	5-HYDROXYTRYPTAMINE 1A RECEPTOR SIGNATURE	PR00512G 6.54 3.139e-06 3-19
359	PD02455	ELEMENT TRANSPOSABLE INSERTION PROTEIN TRANSPOSITION DNA.	PD02455D 18.65 1.000e-05 58-77
360	DM01415	6 SALIVARY GLUE PROTEIN.	DM01415A 6.65 3.250e-07 16-29
361	BL00794	7,8-dihydro-6- hydroxymethylpterin- pyrophosphokinase proteins.	BL00794C 19.62 9.702e-06 27-65
362	PR00866	RNA-DEPENDENT DNA- POLYMERASE (MSDNA) SIGNATURE	PR00866B 9.86 9.786e-06 60-73

^{*} Results include in order: accession number subtype; raw score; p-value; postion of signature in amino acid sequence.

TABLE 4

SEQ ID	pFAM NAME	DESCRIPTION	p-value	pFAM SCORE
2	PGAM	Phosphoglycerate mutase family	2.5e-05	23.4
6	Ubie_methyltran	ubiE/COQ5 methyltransferase family	0.035	-133.9
8	Plexin repeat	Plexin repeat	0.03	18.4
13	K_tetra	K+ channel tetramerisation domain	2.3e-31	117.6
14	EGF	EGF-like domain	7.8e-14	59.4
16	Armadillo_seg	Armadillo/beta-catenin-like repeats	1.3e-05	32.1
19	Ribosomal S5	Ribosomal protein S5	1.7e-46	167.9
21	gpdh	glyceraldehyde 3-phosphate dehydrogenases	1.3e-230	773.2
24	GCV_T	Glycine cleavage T-protein (aminomethyl tran	9.3e-156	530.9
25	zf-C3HC4	Zinc finger, C3HC4 type (RING finger)	0.015	12.5
26	zf-C3HC4	Zinc finger, C3HC4 type (RING finger)	1.6e-10	38.4
33	urease	Urease	0.014	11.0
35	tRNA-synt 1e	tRNA synthetases class I (C)	0.0091	12.1
37	LRRNT	Leucine rich repeat N- terminal domain	0.00049	26.8
39	SH3	SH3 domain	3.4e-60	213.4
40	SH3	SH3 domain	3.4e-60	213.4
41	PBD	P21-Rho-binding domain	1e-08	42.4
42	GDA1_CD39	GDA1/CD39 (nucleoside phosphatase) family	9e-94	324.9
43	Band 7	SPFH domain / Band 7 family	1.7e-21	84.9
46	Rhodanese	Rhodanese-like domain	2.9e-24	94.0
47	zf-C2H2	Zinc finger, C2H2 type	6.2e-32	119.5
50	ZAP	ZAP domain	1.6e-50	181.3
52	sushi	Sushi domain (SCR repeat)	9.5e-27	102.3
55	zf-C2H2	Zinc finger, C2H2 type	0.047	20.3
56	zf-C2H2	Zinc finger, C2H2 type	0.00021	28.1
59	PH	PH domain	2.6e-06	27.6
60	PHD	PHD-finger	2e-09	44.8
64	IQ	IQ calmodulin-binding motif	6.4e-42	152.7
66	ank	Ank repeat	2.7e-23	90.8
69	eIF-1a	Eukaryotic initiation factor 1A	0.0047	-2.4
74	Ribosomal_S17	Ribosomal protein S17	6e-43	148.6
75	LIM	LIM domain containing proteins	0.00067	19.0
80	Phosphodiest	Type I phosphodiesterase / nucleotide py	2.7e-49	177.2
81	transmembrane4	Transmembrane 4 family	6.6e-61	197.7
84	zf-C2H2	Zinc finger, C2H2 type	1.6e-64	227.8
85	zf-C2H2	Zinc finger, C2H2 type	1.4e-07	38.6
89	ank	Ank repeat	4e-31	116.8
93	L15	Ribosomal protein L15	3.5e-21	61.9

ano		DEGCRIPETON	7	T =21/ 00000
SEQ ID NO:	pFAM NAME	DESCRIPTION	p-value	pFAM SCORE
98	Band 41	FERM domain (Band 4.1 family)	0.00015	16.7
101	Noll Nop2 Sun	NOL1/NOP2/sun family	4.5e-19	68.6
103	LIM	LIM domain containing	1.3e-30	113.2
		proteins	1.00 00	110.1
113	WD40	WD domain, G-beta repeat	0.00018	28.3
115	pro isomerase	Cyclophilin type peptidyl-	5.3e-34	120.4
	_	prolyl cis-tr		
116	DUF25	Domain of unknown function DUF25	1.1e-11	46.9
118	Band_41	FERM domain (Band 4.1 family)	3.2e-77	242.4
119	rrm	RNA recognition motif.	1.1e-33	125.4
		(a.k.a. RRM, RBD, or		
120	SH3	SH3 domain	3e-05	30.9
125	Ribosomal_L29	Ribosomal L29 protein	1.6e-15	65.0
126	NTF2	Nuclear transport factor 2 (NTF2) domain	7.6e-06	32.2
129	rrm	RNA recognition motif. (a.k.a. RRM, RBD, or	0.0016	25.2
130	Fork head	Fork head domain	1e-28	108.8
132	PC4	Transcriptional Coactivator	2.1e-38	141.0
		p15 (PC4)		
133	RGS	Regulator of G protein signaling domain	2.6e-45	164.0
137	COX7a	Cytochrome c oxidase subunit	2.3e-40	147.5
139	rrm	RNA recognition motif. (a.k.a. RRM, RBD, or	3.2e-15	64.0
141	lectin c	Lectin C-type domain	5.1e-05	30.0
142	lectin c	Lectin C-type domain	5.1e-05	30.0
147	ig	Immunoglobulin domain	9.1e-07	26.9
150	ank	Ank repeat	8.6e-09	42.6
161	Ribosomal L7Ae	Ribosomal protein L7Ae	0.03	0.8
162	HMG box	HMG (high mobility group) box	8e-53	188.9
163	PH	PH domain	3e-13	52.4
168	Peptidase C6	Helper component proteinase	0.0056	7.9
175	ig	Immunoglobulin domain	2.3e-09	35.2
176	ig	Immunoglobulin domain	9.2e-09	33.3
178	WW	WW domain	0.054	17.2
180	Ribosomal_S12e	Ribosomal protein S12e	1.9e-38	141.1
185	myb_DNA-binding	Myb-like DNA-binding domain	0.00011	29.1
186	myb_DNA-binding	Myb-like DNA-binding domain	0.00011	29.1
187	pkinase	Eukaryotic protein kinase domain	3.4e-26	98.4
189	ER_lumen_recept	ER lumen protein retaining receptor	3.9e-144	492.2
190	ER_lumen_recept	ER lumen protein retaining receptor	2.1e-88	307.1
195	EMP24 GP25L	emp24/gp25L/p24 family	6.9e-06	28.1
199	zf-B box	B-box zinc finger.	5.2e-07	36.7
211	HECT	HECT-domain (ubiquitin-	1.1e-115	397.8
		transferase).		
213	Rhomboid	Rhomboid family	4.2e-42	153.3
214	LIM	LIM domain containing	8.8e-35	127.8
		·		

SEQ ID NO:	pFAM NAME	DESCRIPTION	p-value	pFAM SCORE
		proteins		
215	Ricin_B_lectin	Similarity to lectin domain of ricin	0.0015	19.2
216	chromo	'chromo' (CHRromatin Organization MOdifier	2.1e-09	37.1
218	Sialyltransf	Sialyltransferase family	7.3e-20	79.4
219	PG_binding_2	Putative peptidoglycan binding domain	5e-06	33.5
223	zf-C2H2	Zinc finger, C2H2 type	1.5e-104	360.7
226	RGS	Regulator of G protein signaling domain	5.1e-52	186.2
227	TBC	TBC domain	7.2e-35	129.3
228	CRAL TRIO	CRAL/TRIO domain.	4.5e-47	158.6
232	Ribosomal L44	Ribosomal protein L44	1e-48	175.3
235	ig	Immunoglobulin domain	3.5e-08	31.4
236	thyroglobulin 1	Thyroglobulin type-1 repeat	3.9e-24	93.6
238	TBC	TBC domain	1.2e-54	195.0
241	zf-C2H2	Zinc finger, C2H2 type	3.8e-08	40.5
242	AAA	ATPases associated with various cellular act	2.1e-43	157.6
249	integrin_A	Integrin alpha cytoplasmic region	0.091	18.0
256	PAP2	PAP2 superfamily	0.00084	22.8
257	zf-C2H2	Zinc finger, C2H2 type	1.2e-60	214.9
259	G-gamma	GGL domain	5.5e-30	108.3
266	efhand	EF hand	3.4e-07	37.4
267	efhand	EF hand	3.4e-07	37.4
274	zf-C2H2	Zinc finger, C2H2 type	0.00014	28.6
277	RecF	RecF protein	0.036	11.1
281	CH	Calponin homology (CH) domain	7.9e-22	86.0
285	cyclin	Cyclin	3.9e-07	28.5
289	zf-C2H2	Zinc finger, C2H2 type	1.9e-21	84.7
290	PI-PLC-X	Phosphatidylinositol-specific phospholipase	0.073	10.8
299	60s_ribosomal	60s Acidic ribosomal protein	4.1e-07	25.8
307	trypsin	Trypsin	6.9e-81	257.3
310	ig	Immunoglobulin domain	1.3e-10	39.3
311	ig	Immunoglobulin domain	6.1e-07	27.4
313	globin	Globin	3.8e-21	78.2
315	ig	Immunoglobulin domain	1.6e-05	22.8
318	zf-C2H2	Zinc finger, C2H2 type	9e-19	75.8
319	ig	Immunoglobulin domain	0.01	13.8
320	BTB	BTB/POZ domain	5e-17	70.0
322	aa permeases	Amino acid permease	0.0058	-262.2
325	ig	Immunoglobulin domain	1.6e-10	38.9
327 328	ig	Immunoglobulin domain	1.9e-09	35.5
328	ig	Immunoglobulin domain	2.9e-09	34.9
332	ig Ribosomal L36e	Immunoglobulin domain	7.4e-14	49.7
333	connexin	Ribosomal protein L36e	6.3e-17	69.7
335	p450	Connexin	7.6e-148	504.6
337	Sm Sm	Cytochrome P450 Sm protein	2.1e-100	347.0
338	zf-C2H2	Zinc finger, C2H2 type	0.00012	28.8
220	41 CC11C	Tine Tinger, CZHZ type	0.0025	24.5

SEQ ID	pFAM NAME	DESCRIPTION	p-value	pFAM SCORE
NO:				
343	aldo ket red	Aldo/keto reductase family	2.4e-53	190.7
345	ubiquitin	Ubiquitin family	3.1e-13	45.5
346	СН	Calponin homology (CH) domain	0.0017	23.8
351	ig	Immunoglobulin domain	4.8e-18	63.2
352	iq	Immunoglobulin domain	4.8e-18	63.2
358	G-alpha	G-protein alpha subunit	4.5e-148	505.3
359	iq	Immunoglobulin domain	8.9e-09	33.3
362	Ribosomal_L37ae	Ribosomal L37ae protein family	0.00083	-3.0

TABLE 5

SEQ ID NO:	POSITION OF SIGNAL IN AMINO ACID	maxS (MAXIMUM SCORE)	meanS (MEAN SCORE)
	SEQUENCE	0.040	0.664
2	1-29	0.942	0.664
12	1-15	0.909	0.589
14	1-17	0.974	0.943
20	1-22	0.932	0.802
25	1-16	0.988	0.881
28	1-13	0.896	0.771
37	1-21	0.992	0.929
42	1-46	0.978	0.754
52	1-34	0.954	0.756
63	1-31	0.960	0.773
71	1-45	0.981	0.652
80	1-22	0.982	0.882
81	1-42	0.993	0.715
83	1-30	0.966	0.767
95	1-18	0.997	0.971
102	1-13	0.981	0.764
107	1-45	0.890	0.631
110	1-27	0.992	0.969
138	1-33	0.961	0.864
144	1-45	0.987	0.658
145	1-20	0.992	0.967
175	1-20	0.957	0.874
176	1-21	0.989	0.945
179	1-42	0.980	0.577
184	1-20	0.972	0.771
189	1-28	0.941	0.755
190	1-28	0.941	0.755
191	1-12	0.907	0.779
195	1-21	0.958	0.779
200	1-15	0.970	0.875
211	1-20	0.895	0.595
215	1-31	0.987	0.895
218	1-30	0.971	0.889
225	1-17	0.884	0.588
235	1-23	0.965	0.817
237	1-29	0.933	0.725
249	1-28	0.972	0.870
251	1-17	0.966	0.905
260	1-26	0.921	0.587
270	1-20	0.938	0.631
283	1-18	0.901	0.763
288	1-20	0.940	0.693
293	1-26	0.937	0.784
295	1-22	0.972	0.745
296	1-15	0.930	0.748
297	1-35	0.906	0.600
300	1-29	0.981	0.864
307	1-19	0.976	0.916
308	1-27	0.973	0.931

SEQ ID NO:	POSITION OF SIGNAL	maxS (MAXIMUM	meanS (MEAN SCORE)
	IN AMINO ACID	SCORE)	
	SEQUENCE		
309	1-29	0.950	0.629
310	1-19	0.969	0.913
311	1-21	0.956	0.823
315	1-17	0.976	0.938
317	1-19	0.943	0.837
319	1-18	0.991	0.978
324	1-26	0.968	0.806
325	1-20	0.972	0.828
326	1-27	0.893	0.567
327	1-21	0.994	0.959
328	1-20	0.945	0.891
329	1-21	0.984	0.858
330	1-27	0.891	0.593
333	1-40	0.955	0.703
347	1-22	0.968	0.806
351	1-23	0.982	0.945
352	1-23	0.982	0.945
355	1-32	0.955	0.617
356	1-23	0.936	0.677
359	1-20	0.937	0.859
360	1-29	0.956	0.765
361	1-23	0.968	0.819

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CLAIMS

WHAT IS CLAIMED IS:

- 1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-362, a mature protein coding portion of SEQ ID NO: 1-362, an active domain of SEQ ID NO: 1-362, and complementary sequences thereof.
- 2. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide hybridizes to the polynucleotide of claim 1 under stringent hybridization conditions.
- 3. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide has greater than about 90% sequence identity with the polynucleotide of claim 1.

4. The polynucleotide of claim 1 wherein said polynucleotide is DNA.

5. An isolated polynucleotide of claim 1 wherein said polynucleotide comprises the complementary sequences.

6. A vector comprising the polynucleotide of claim 1.

- 7. An expression vector comprising the polynucleotide of claim 1.
- 25 8. A host cell genetically engineered to comprise the polynucleotide of claim 1.
 - 9. A host cell genetically engineered to comprise the polynucleotide of claim 1 operatively associated with a regulatory sequence that modulates expression of the polynucleotide in the host cell.
 - 10. An isolated polypeptide, wherein the polypeptide is selected from the group consisting of:
 - (a) a polypeptide encoded by any one of the polynucleotides of claim 1; and

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- (b) a polypeptide encoded by a polynucleotide hybridizing under stringent conditions with any one of SEQ ID NO: 1-362.
- 11. A composition comprising the polypeptide of claim 10 and a carrier.

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- 12. An antibody directed against the polypeptide of claim 10.
- 13. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form the complex; and
- b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected.
- 15 14. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
 - a) contacting the sample under stringent hybridization conditions with nucleic acid primers that anneal to the polynucleotide of claim 1 under such conditions;
 - b) amplifying a product comprising at least a portion of the polynucleotide of claim 1; and
 - c) detecting said product and thereby the polynucleotide of claim 1 in the sample.
- The method of claim 14, wherein the polynucleotide is an RNA molecule and
 the method further comprises reverse transcribing an annealed RNA molecule into a cDNA polynucleotide.
 - 16. A method for detecting the polypeptide of claim 10 in a sample, comprising:
 - a) contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex; and
 - b) detecting formation of the complex, so that if a complex formation is detected, the polypeptide of claim 10 is detected.

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- 17. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
- a) contacting the compound with the polypeptide of claim 10 under conditions sufficient to form a polypeptide/compound complex; and
- b) detecting the complex, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.
- 18. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
 - a) contacting the compound with the polypeptide of claim 10, in a cell, under conditions sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and
 - b) detecting the complex by detecting reporter gene sequence expression, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.
 - 19. A method of producing the polypeptide of claim 10, comprising,
 - a) culturing a host cell comprising a polynucleotide sequence selected from the group consisting of a polynucleotide sequence of SEQ ID NO: 1-362, a mature protein coding portion of SEQ ID NO: 1-362, an active domain of SEQ ID NO: 1-362, complementary sequences thereof and a polynucleotide sequence hybridizing under stringent conditions to SEQ ID NO: 1-362, under conditions sufficient to express the polypeptide in said cell; and
 - b) isolating the polypeptide from the cell culture or cells of step (a).
 - 20. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of any one of the polypeptides from the Sequence Listing, the mature protein portion thereof, or the active domain thereof.
 - 21. The polypeptide of claim 20 wherein the polypeptide is provided on a polypeptide array.

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- 22. A collection of polynucleotides, wherein the collection comprising the sequence information of at least one of SEQ ID NO: 1-362.
- 23. The collection of claim 22, wherein the collection is provided on a nucleic acid array.
 - 24. The collection of claim 23, wherein the array detects full-matches to any one of the polynucleotides in the collection.
- 10 25. The collection of claim 23, wherein the array detects mismatches to any one of the polynucleotides in the collection.
 - 26. The collection of claim 22, wherein the collection is provided in a computer-readable format.
 - 27. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.
- 28. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising an antibody that specifically binds to a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.

ABSTRACT OF THE INVENTION

The present invention provides novel nucleic acids, novel polypeptide sequences encoded by these nucleic acids and uses thereof.

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Express Mail No.: . EF415382545US

Docket No.: 797

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As [a] below named inventor(s), I/we hereby declare that:

Y. Tom Tang, Ping Zhou, Ryle Goodrich, Chenghua Liu, Vinod Asundi, Feiyan Ren, Jie Zhang, Qing A. Zhao, Aidong J. Xue, Yonghong Yang, Tom Wehrman, Radoje T. Drmanac

My/our residence, post office address and citizenship is/are as stated below next to my/our name(s).

I/we believe I/we am/are an/the original, first and sole/joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: NOVEL NUCLEIC ACIDS AND POLYPEPTIDES, the specification of which

<u>X</u>	is attached hereto.	
	was filed on [date] as Application Serial Number [and was amended on [date].]

I/We hereby state that I/we have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I/We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I/We hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate, listed below and so identified, and I/we have also identified below any foreign application for patent or inventor's certificate on this invention filed by me or my legal representatives or assigns and having a filing date before that of the application on which priority is claimed:

NUMBER	COUNTRY	DAY/MONTH/ YEAR FILED	PRIORITY CLAIMED - YES OR NO

I/We hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I/we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

SERIAL NUMBER	FILING DATE	STATUS	

I/We hereby declare that all statements made herein of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I/We hereby appoint the following attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith and request that all correspondence and telephone calls with respect to this application be directed to Leslie A. Mooi, HYSEQ, INC., 670 Almanor Avenue, Sunnyvale, CA 94085, Telephone No. (408) 524-8100:

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Full name of fifth joint inventor: Inventor's signature:	Vinod Asundi	
•	Date:	
Residence and Post Office Address:	709 Foster City Blvd., Foster City, CA 94404	
Citizenship:	United States of America	
Full name of sixth joint inventor:	Feiyan Ren	
Inventor's signature:	Date:	
Residence and Post Office Address:	20685 Garden Manor Court, Cupertino, CA 95014	
Citizenship:	People's Republic of China	

Full name of seventh joint inventor:	Jie Zhang
Inventor's signature:	Date:
Residence and Post Office Address:	20800 Homestead Road, #38B, Cupertino, CA 95014
Citizenship:	People's Republic of China
Full name of eigth joint inventor:	Qing A. Zhao
Inventor's signature:	Date:
Residence and Post Office Address:	1028 S. de Anza Blvd., Apt. B-210, San Jose, CA 95129
Citizenship:	People's Republic of China
Full name of ninth joint inventor:	Aidong J. Xue
Inventor's signature:	Date:
Residence and Post Office Address:	1621 S. Mary Avenue, Sunnyvale, CA 94087
Citizenship:	People's Republic of China
Full name of tenth joint inventor:	Yonghong Yang
Inventor's signature:	Date:
Residence and Post Office Address:	4230 Ranwick Ct, San Jose, CA 95118
Citizenshin:	United States of America

Full name of eleventh joint inventor:	Tom Wehrman
Inventor's signature:	Date:
Residence and Post Office Address:	300 Pasteur Drive, Edwards R314, Stanford University Medical Center, Stanford, CA 94305
Citizenship:	United States of America
Full name of twelfth joint inventor:	Radoje T. Drmanac
Inventor's signature:	Date:
Residence and Post Office Address:	850 East Greenwich Place, Palo Alto, CA 94303
Citizenship:	Yugoslavia

Express Mail No.: EF415382545US Docket No.: 797

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Tang, et al.

Serial No: Not Yet Assigned

Filed: Herewith

For: NOVEL NUCLEIC ACIDS

AND POLYPEPTIDES

CERTIFICATE OF MAILING
BY "EXPRESS MAIL" UNDER 37 CFR § 1 10

"Express Mail" Mailing Label Numbers EF415382559US

Date of Deposit November 17, 2000

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Type or Print Name of Person Mailing. Sandy Fong

STATEMENT REGARDING SEQUENCE LISTING UNDER 37 CFR §1.821(f)

Signature of Person Mailing

BOX PATENT APPLICATION Assistant Commissioner for Patents Washington, D.C. 20231

Dear Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 CFR §1.821(c) and (e), respectively, are the same.

Respectfully submitted,

Dated: November 17, 2000

By: _

Leslie A. Mooi ⁶ Attorney for Applicants Registration No.: 37,047

HYSEQ, INC.

670 Almanor Avenue Sunnyvale, CA 94085

SEQUENCE LISTING

	Tang, Y. T	om				
	u, Ping drich, Ryle					
	, Chenghua					
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8

649

697

170

165

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180

145

160

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	gag atc aga gca aat Glu Ile Arg Ala Asn 490		
	gcc aca gac att gtg Ala Thr Asp Ile Val 505		
	cat ctc cac aat taa His Leu His Asn * 520	ctcct atcagaacca tcg	gattttc 1645
tgctgtattt ttctg	ggaaag aaaactttct tta	eccactt ataaacagaa g	actgtgaca 1705
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tcctgcatag ttta	ttaaaa aaaattagtc gta	aaattta teetteaaaa a	tctgcattt 1825
taaataaacc ctgad	cagtga tttctcaaga ctg	taaagat attagtctga g	aatgcaact 1885
ctaacagact gctct	tgggca tettttetet ttg	ccttggc caggcctctc a	gaattgagt 1945
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	tcc ggg ggt tgg ttt Ser Gly Gly Trp Phe: 10		
	aaa gct gcg cgt ccc Lys Ala Ala Arg Pro : 30		
	ctc agt ggg act cta Leu Ser Gly Thr Leu 45		

			-			tgg Trp 60						_				245	
						agt Ser							_	_		293	
						gtc Val										341	
						tgg Trp										389	
						agg Arg						_			_	437	
						cag Gln 140										485	
						ggt Gly										533	
						att Ile										581	
						aaa Lys										629	
						tcc Ser										677	
						gta Val 220					_					725	
						cag Gln										773	
						aca Thr										821	
						gag Glu										869	
act	cat	aca	tgg	gag	aag	ttt	gtt	tca	cct	gaa	aca	cta	gag	agc	att	917	

Thr His Thr Trp Glu Lys Phe Val Ser Pro Glu Thr Leu Glu Ser Ile 280 285 290													
ctg gaa tca aat ggt ctg tca gtt caa aca gtg gta gga atg ctc tat Leu Glu Ser Asn Gly Leu Ser Val Gln Thr Val Val Gly Met Leu Tyr 295 300 305	965												
aac ccc ttc tca ggt tac tgg cat tgg agt gaa aat acc agc ctt aac Asn Pro Phe Ser Gly Tyr Trp His Trp Ser Glu Asn Thr Ser Leu Asn 310 325	1013												
tat gca gct cat gct gtg aaa tcc agg gtc cag gaa cac cca gcc tct Tyr Ala Ala His Ala Val Lys Ser Arg Val Gln Glu His Pro Ala Ser 330 335 340	1061												
gct gag ttt gtt tta aag gga gaa aca gaa gag ctc caa gct aat gcc Ala Glu Phe Val Leu Lys Gly Glu Thr Glu Glu Leu Gln Ala Asn Ala 345 350 355	1109												
tgc acc aat cca gct gtg cat gaa aag ctg aag aaa tga attgtttctg Cys Thr Asn Pro Ala Val His Glu Lys Leu Lys Lys * 360 365 370	1158												
agaactatag taatatggct tggatatctg atgttttcaa atacaagaaa tgtacaattt	1218												
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		_		_		-	-		-	_	gta Val					320
_	-			_				-	-		gaa Glu		_	_		368
_						_	_	_	-		aat Asn	_	_		_	416
		_	_		-	_	_		_		cgg Arg 95	-			_	464
_		_	-	_		_	_				gag Glu			_		512
_	_				_	-			_	_	aat Asn	_		-		560
		_		-			_				cag Gln	-			_	608
_						_	_				att Ile					656
	_			~	-		_		-	-	ata Ile 175	_				704
											gag Glu					752
-	-	-	_		_					_	tca Ser	_	_		_	800
				_	_		_				ggg ggg					848
											cgt Arg					896
		_	-	_							tcg Ser					944

						tta Leu		-		-	-		-			992
-	_	-	-	-		caa Gln			-							1040
_		_			-	ata Ile	-	_								1088
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_			_			aca Thr 330										1184
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				~		ttg Leu					_		-		-	1280
_		_			_	aaa Lys		-	_	_						1328
						agg Arg										1376
			_	_		gtt Val 410			-							1424
				_	-	agg Arg		_	_		_					1472
			_			acc Thr							_	_		1520
~		-	_	_		gag Glu		_			-			-	-	1568
	_	_	_		_	gct Ala		_	_		_	-		-		1616

_		_			-					-	cag Gln 495		_		_		1664
_		_			-		-			_	agg Arg	_			-		1712
-	_	-		_	-			_		_	ctc Leu		_				1760
_				_	_	-	_		_		gtg Val	_		_	_		1808
											agt Ser						1856
		_	_			_	~				tta Leu 575			_	•		1904
											cta Leu						1952
-			~			•	_	-	-		cgt Arg	-					2000
-				-		-	-		_		aag Lys		-				2048
-		-		-	_	-	-	-			atc Ile	_			_		2096
_	_	_			_	_		_			gaa Glu 655		_				2144
_	-	_	-	-		-	-			_	aaa Lys	_	_	_	_		2192
											atg Met					:	2240
		_	_	-		-		-	-	_	tat Tyr			-		:	2288

	aga Arg			_								_				2336
	gca Ala 725	_		-				_	_						-	2384
	agc Ser															2432
_	aac Asn						_			_	_	_			-	2480
_	gaa Glu		-	_	_	_		_	-							2528
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	aga Arg		_		_	_		_								2672
_	gag Glu		-	-	_	_				_						2720
_	gga Gly	_	_		_		_		-			-				2768
•	gat Asp							_	~ ~		_	_	_	_		2816
	cag Gln 885		_				_	_	_			_		_		2864
	ctg Leu		-		_		_	-	_		-	-	_			2912
-	tta Leu			taa * 920	aaat	gcat	itt g	gcaaa	ggga	ig aa	aatg	gaagg	g cca	aaca	agaa	2967
gcag	ggcto	cca g	ctto	tgca	aa aa	actt	ggat	tca	caaa	tgt	ccct	gaac	ag a	aaat	gaagc	3027

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<213> Homo sapiens

<220> <221> CDS

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ttcaaaccct tcggcaccgt gtcctggctg aggaggacgg cgtccctgac acctgacccc 180
ttctgtccca cacacctcac ctgcctgcag agttgccttc tcctgcacgc ctctctttt 240
ctcaccaagc ctgctcctca ttccctggag tgcccctgag cccatgtgtc cgccctcctg 300
cagaac atg gag aac ttc acc ctg gca agg gac gag aag ggg aat gtc
Met Glu Asn Phe Thr Leu Ala Arg Asp Glu Lys Gly Asn Val

	_	_	_		_	ggc Gly	_	_			_	_			_	396
		-	_		_	gat Asp								-	-	444
_					_	ccg Pro	-		_		_		_		_	492
		-			-	tcc Ser				-		-		-		540
						cct Pro 85										588
_	_	_				ttc Phe		-				_	-			636
						gtg Val										684
						gtg Val										732
-	-	-		_	-	tca Ser			-	-						780
	_	_	_	-		acg Thr 165	-	_		_		_	_		_	828
						gtc Val										876
	_	~ ~		_	•	tgt Cys	_			_	_	_		_	-	924
						aag Lys										972
					_	gtg Val								_		1020
acc	aac	agt	gcc	cgg	gaa	agg	aag	atc	aac	tca	tcc	ctg	cag	ctc	cca	1068

Thr	Asn 240	Ser	Ala	Arg	Glu	Arg 245	Lys	Ile	Asn	Ser	Ser 250	Leu	Gln	Leu	Pro	
~	_		_		ttc Phe 260		_	_			-	-	_		_	1116
					ctg Leu											1164
	-	-		-	gtc Val			_					-			1212
	_				gac Asp					_	-		_			1260
					att Ile			_	_				_		_	1308
					ctc Leu 340											1356
_			_		gta Val	-	_			-	-		_	_	_	1404
		-	_		gac Asp	_										1452
	_			_	tgc Cys	_		-	-			_		_	_	1500
					atc Ile											1548
	_	_			tcg Ser 420	_			_			_				1596
					caa Gln											1644
					ctc Leu											1692
		-		-	aat Asn	-	_	_		-						1740

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<220> <221> CDS <222> (44)..(1168)

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Gln Val Ala Glu Ser Asp Leu Ser Asp Gly Lys Ala Ser Leu Val
25 30 35

agc gag gaa gag gaa gat gaa gaa gat aag gct acc cct aga aga 199

Ser	Glu	Glu	Glu 40	Glu	Asp	Glu	Glu	Glu 45	Asp	Lys	Ala	Thr	Pro 50	Arg	Arg	
					agt Ser											247
		_	_	_	gcc Ala				-			_				295
					gca Ala 90											343
					tgt Cys											391
			_	_	gac Asp			_	_		_		_		_	439
	_	_			acc Thr	-		_	_					_		487
-	-		_		gaa Glu											535
_					gct Ala 170			_	_					_		583
_					acg Thr		_	_					_			631
					gct Ala											679
		_	-		tac Tyr	_		_	_		_				~~~	727
	_		~ ~		aga Arg	_	_		_							775
					gaa Glu 250											823
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	265	270	275	
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			ctg cgg aac cgc tat Leu Arg Asn Arg Tyr 305	967
		Leu Asp Pro A	gat tgg gtg tgt ccc Asp Trp Val Cys Pro 320	1015
			cgg aag cgt gac ggc Arg Lys Arg Asp Gly 340	1063
			aag ttt tat ggt tat Lys Phe Tyr Gly Tyr 355	1111
	Glu Tyr Leu Glu	-	aag gag ctg gta gaa Lys Glu Leu Val Glu 370	1159
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gcc ggc ccc att cca gaa gca gag acc agg gga gcc aag aga att tcc

557

Ala	Gly	Pro	Ile 40	Pro	Glu	Ala	Glu	Thr 45	Arg	Gly	Ala	Lys	Arg 50	Ile	Ser	
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~ ~	_		_		tcc Ser	-				-	-	_		_		653
		_		_	acc Thr 90		_	-					_	_		701
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					tcc Ser											845
		_			ccg Pro			-								893
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					ccc Pro											989
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			cct ccg act ac Pro Pro Thr Th 46	nr Thr Asn Ser
		-	aag atc aca ac Lys Ile Thr Th 480	
	_	_	ccc acg act gc Pro Thr Thr Al 495	

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Asp 5	Thr	Glu	Val	Pro	Ala 10	Met	Thr	Leu	Ala	Pro 15	Gly	His	Ala	Ala	Leu 20	
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	_	_				-								ttc Phe	_	605
														agc Ser		653
														gat Asp		701
	_	-			_									gaa Glu 115		749
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~	~	~		_				-	_	_			-	ggc Gly		845
		_												act Thr		893
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														aag Lys 155		781
_									_		-		_	ttg Leu		829
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		Ser His Pro	cta gaa ggc gac Leu Glu Gly Asp 95	
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			aaa Lys						919
			gat Asp						967
			ggc Gly						1015
			tgt Cys						1063
			cct Pro 265						1111
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			ggt Gly						1255
			gtg Val						1303
			atc Ile 345						1351
			ctg Leu						1399
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cca ttc a	_				_	_				_				1495
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att gag of Ile Glu 1														1591
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ctc atc c														1687
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cag acg Gln Thr		Gly										tag *	ttc	1927
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		gag acc ctg Glu Thr Leu		-	55 55	540
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		gag ctg acc Glu Leu Thr 135	-		5 5	732
		tcg gcc agc Ser Ala Ser			5 5	780
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acaaaaatgg tacccacgtg ggcatggaaa tggggcagat taggggacca ctggactcag	2009
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<213> Homo sapiens

<220>

<221> CDS

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atg aac agc cgt ggc atc tgg ctc tcc tac gtg ctg gcc atc ggt ctc Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu 20 25 30	214
ctc cac atc gtg ctg ctg agc atc ccg ttt gtg agt gtc cct gtc gtc Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val 35 40 45	262
tgg acc ctc acc aac ctc att cac aac atg ggc atg tat atc ttc ctg Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 50 55 60	310
cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag gcg His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala 65 70 75 80	358
agg ctg cta acc cac tgg gag cag atg gat tat ggg gtc cag ttc acg Arg Leu Leu Thr His Trp Glu Gln Met Asp Tyr Gly Val Gln Phe Thr 85 90 95	406
gcc tct cgg aag ttc ttg acc atc aca ccc atc gtg ctg tac ttc ctc Ala Ser Arg Lys Phe Leu Thr Ile Thr Pro Ile Val Leu Tyr Phe Leu 100 105 110	454
acc agc ttc tac act aag tac gac cag atc cat ttt gtg ctc aac acc Thr Ser Phe Tyr Thr Lys Tyr Asp Gln Ile His Phe Val Leu Asn Thr 115 120 125	502
gtg tcc ctg atg agc gtg ctt atc ccc aag ctg ccc cag ctc cac gga Val Ser Leu Met Ser Val Leu Ile Pro Lys Leu Pro Gln Leu His Gly 130 135 140	550
gtc cgg att ttt gga atc aat aag tac tga g agtgcagccc cttcccctgc Val Arg Ile Phe Gly Ile Asn Lys Tyr * 145 150	601
ccagggtggc aggggagggg tagggtaaaa ggcatgtgct gcaacactga agacagaaag	661
aagaageete tggacaetge cagagatggg ggttgageet etggeetaat tteeeceete	721
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<211> 1605

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<213> Homo sapiens

<220>

<221> CDS

<222> (535)..(1050)

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gctggtaact ttggcgcctc cgccaagccc tgccagactc ccctggctgt gatggcattc
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gcatgagcca tgtgcttctt tgcccttctc tgtcctgttc caatcttctg cctcccagtc	420
actecetggg gactatggga teactgtece eccacetgtg tggccacace atgtgtectg	480
tcaatccaga actgcctctg agetccagge tgaccacaga tcagccacag cctg atg Met 1	537
cct gca gcc cca ctt tgc tca ccc ttc ccc tcc cct cct tcc ttc Pro Ala Ala Pro Leu Cys Ser Pro Phe Pro Ser Pro Pro Pro Ser Phe 5 10 15	585
cac aca gca agc cta cct ttc tcc atc cat gct cac cat agc ccc ctt His Thr Ala Ser Leu Pro Phe Ser Ile His Ala His His Ser Pro Leu 20 25 30	633
cct tgt gac ttg gac cct cca ttg tac ctg gct gag act gtc agc ctc Pro Cys Asp Leu Asp Pro Pro Leu Tyr Leu Ala Glu Thr Val Ser Leu 35 40 45	681
ctg gag gag tgg ggt cca cct tct tct tgc cct atg cag tgc aag ctc Leu Glu Glu Trp Gly Pro Pro Ser Ser Cys Pro Met Gln Cys Lys Leu 50 55 60 65	729
act tct cac cca gca agg ttg act cat ctg cct cca tgt ctc tgg ggc Thr Ser His Pro Ala Arg Leu Thr His Leu Pro Pro Cys Leu Trp Gly 70 75 80	777
ttt gct gtt gcc ctg aaa cct agc tgg gct ggt ctt gct ccc agc ttg Phe Ala Val Ala Leu Lys Pro Ser Trp Ala Gly Leu Ala Pro Ser Leu 85 90 95	825
ctt ccc cct ccg atg tcc ctt tgc agg ccc ctg tcg ttc ctc cgg Leu Pro Pro Pro Arg Met Ser Leu Cys Arg Pro Leu Ser Phe Leu Arg 100 105 110	873
cac cag tgt cct tgg ctg cca tgg caa gct cat cag ggg ctt gta ccc His Gln Cys Pro Trp Leu Pro Trp Gln Ala His Gln Gly Leu Val Pro 115 120 125	921
tgg tca cca agc atg gta gca gct gcc tgc att gta tct cca tct ggt Trp Ser Pro Ser Met Val Ala Ala Ala Cys Ile Val Ser Pro Ser Gly 130 135 140 145	969
cac tgc agg tgc caa ccc ttc atc ccc cat gtt ttc ctg ggc cat gga His Cys Arg Cys Gln Pro Phe Ile Pro His Val Phe Leu Gly His Gly 150 155 160	1017
ggg ctg acc tcc gtt tct ggg gaa tgt ggc tga gctgtggt aaccagctac Gly Leu Thr Ser Val Ser Gly Glu Cys Gly * 165 170	1068
accccaggtg ctctttccat ggtggtgcct gctcatcttg ctgatgcaaa ctaggaagtt	1128

1188 aggetgeate teggagtgge tttegetgga gaggtgettt getgtetete agaeteagte actgtgttcc ctccccgcct ctcttatctc catggctgtt tgcagctctc ccaggtactt 1248 tggggtctga gctggaattc ctttgtggtt tgctcttctg cttctcactc ttgtattaag 1308 1368 aaggattcca caaagggaga gtggcatccc tgctgctgct gtgccagacc agagtttcct gaggggccct gaccctaacc ctccagctca gccctgtaca cctgaccctg taaatgagtg 1428 1488 gggtttgctg actgtaatcc ctgacaccag taaaaccaaa aggactcttg ggggctcagt 1548 gtgagagcca gggttaccta ctctgccaag tgaggacaaa ctgctaggct gtatcccata 1605 atttcaggat gagaaacatt aacaataaaa atttgtagta aacataaaaa aaaaaaa

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Gly Gly Pro Gly Gly Pro Gly Met Gly Asn Arg Gly Gly 20 10 15 ttc cgc gga ggt ttc ggc agt ggc atc cgg ggc cgg ggt cgc ggc cgt 329 Phe Arg Gly Gly Phe Gly Ser Gly Ile Arg Gly Arg Gly Arg Gly Arg

25 377 gga cgg ggc cgg ggc cga ggc cgc gga gct cgc gga ggc aag gcc gag Gly Arg Gly Arg Gly Arg Gly Ala Arg Gly Gly Lys Ala Glu 50 55 45

35

30

gat aag gag tgg atg ccc gtc acc aag ttg ggc cgc ttg gtc aag gac 425 Asp Lys Glu Trp Met Pro Val Thr Lys Leu Gly Arg Leu Val Lys Asp 70 60 65

473 atg aag atc aag tcc ctg gag gag atc tat ctc ttc tcc ctg ccc att

Met	Lys	Ile 75	Lys	Ser	Leu	Glu	Glu 80	Ile	Tyr	Leu	Phe	Ser 85	Leu	Pro	Ile	
											gcc Ala 100					521
											acc Thr					569
											gac Asp					617
_		-		-	_	-		_			gcc Ala		_		-	665
				_	_	_				_	ccc Pro		_	_		713
				_			_				gtc Val 180		~	_		761
											cat His					809
											cca Pro					857
											ccc Pro					905
									_	_	gat Asp			_	_	953
							_				cag Gln 260		_		_	1001
											cct Pro					1049
											caa Gln					1097
											atg Met	-	-	_	_	1145

	300	305		310	
	ggc agg gag Gly Arg Glu		atcac ca	ctccaggg acttaga	itct 1197
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gccgcagacc	accaggccac c	agagtgcac ag	catgcaca	gaaacactgc cgcag	gaagc 1377
acacacagcg	gcttcccaca t	cacaagggc ca	caatgggc	ccccagggcc cacco	ecgctg 1437
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gccgctatta	ccactgaacc c	ggaccccct ac	ccaggtcc	agggccagcc gcc	atg 116 Met 1
acg aac gtg Thr Asn Val	tac tcc ttg Tyr Ser Leu 5	gat ggg att Asp Gly Ile 10	Leu Val	ttt ggt ttg ctc Phe Gly Leu Leu 15	ttt 164 Phe
	Cys Ala Tyr			cgt ctc aaa acc Arg Leu Lys Thr 30	
				ttt tac aaa gcc Phe Tyr Lys Ala 45	
gtg att gga Val Ile Gly 50	acc agg ctg Thr Arg Leu 55	His Ala Ala	gtg gca Val Ala 60	att gct tgt gtt Ile Ala Cys Val	gta 308 Val 65
atg gcc ttt	tac gtc ctg	ttt ata aaa	tga a tt	ccaaagca cccaagt	ccat 359

caactgccaa ccaaggggac ggggatgaag aacctgttgg agacctgaac ccagtgtagg

479 agagttcagc tgaaatcatc ggtccccagg atgacaccac agcatctgcc cctgctatat gtggggaaaa ctcatggtca cgaacattat ttatgcttca ggggactaca gaaagccagc 539 ttcctttgat ctatgtgtaa atcagtcctt ggcagagtgc atataatgtc cggataaatt 599 acacccctcg gtgataagat tacatacctc cttcataaaa acctgtcatc ctgtttgttc 659 719 ttcagctcct catcaggatc ttttcaaact gggctcatta gggaaggaac taggcttgtg 779 ttcagacttc tttgagagcg agaatttcca gacttctttt cctccttgat tggtctggca 839 ttggggcggg gatgctgggt gggaacccgt ttgaattgcc aggaaattct tgggttagaa ttctcttcat gtccatccgg accttaggag gctggggctt gcaaggaccc gtcctcccgg 899 907 ttggccgg <210> 21 <211> 1329 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (103)..(1116) <400> 21 60 aaqqatcctt aattaaatta atccccccc ccggctcctc ctgttcgaca gtcagccgca 114 tcttcttttg cgtcgccagc cgagccacat cgctcagaca cc atg ggg aag gtg Met Gly Lys Val 1 aag gtc gga gtc aac gga ttt ggt cgt att ggg cgc ctg gtc acc agg 162 Lys Val Gly Val Asn Gly Phe Gly Arg Ile Gly Arg Leu Val Thr Arg 10 gct gct ttt aac tct ggt aaa gtg gat att gtt gcc atc aat gac ccc 210 Ala Ala Phe Asn Ser Gly Lys Val Asp Ile Val Ala Ile Asn Asp Pro

gct gct ttt aac tct ggt aaa gtg gat att gtt gcc atc aat gac ccc 210
Ala Ala Phe Asn Ser Gly Lys Val Asp Ile Val Ala Ile Asn Asp Pro
25 30 30 35

ttc att gac ctc aac tac atg gtt tac atg ttc caa tat gat tcc acc
Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln Tyr Asp Ser Thr
40 45 45 50

cat ggc aaa ttc cat ggc acc gtc aag gct gag aac ggg aag ctt gtc
His Gly Lys Phe His Gly Thr Val Lys Ala Glu Asn Gly Lys Leu Val
55 60 60 65

atc aat gga aat ccc atc acc atc ttc cag gag cga gat ccc tcc aaa
354

Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg Asp Pro Ser Lys
70 75 80

													tcc Ser			402
_				_	-	_	_		-		_	_	ggg Gly			450
													atg Met 130			498
_	-					_		_		_		_	atc Ile		_	546
													aag Lys			594
	-						_			_			gtc Val			642
		-											gga Gly			690
													cct Pro 210			738
		_	_	_	_	_		_	_				ctg Leu			786
													gtg Val			834
	_	-		_	_		-			_			gat Asp			882
													ggc Gly			930
													agc Ser 290			978
					-	-		_			-		aac Asn			1026
ttt	gtc	aag	ctc	att	tcc	tgg	tat	gac	aac	gaa	ttt	ggc	tac	agc	aac	1074

Phe Val Lys Leu Ile Ser Trp Tyr Asp Asn Glu Phe Gly Tyr Ser Asn 310 315 320	
agg gtg gtg gac ctc atg gcc cac atg gcc tcc aag gag taa gacccct Arg Val Val Asp Leu Met Ala His Met Ala Ser Lys Glu * 325 330 335	1123
ggaccaccag ccccagcaag agcacaagag gaagagagag	1183
cctgccacac tcagtccccc accacactga atctcccctc ctcacagttg ccatgtagac	1243
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gacagttctg ggtgtagagg actcacatcc cagagaggct gaggaagggt ttaccaccgc	240
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ctageteect gecagettee tgteeetgtg etcaetgeee ecaegeetee tgecaaggee	480
gagccacaca cccgctccac ctgcatttcc tctaccgact cgccagccca a atg ccg Met Pro 1	537
ctc ttc act ctg gcc tcg ctg agc ggc tgc ccg agg agg agc tct agg Leu Phe Thr Leu Ala Ser Leu Ser Gly Cys Pro Arg Arg Ser Ser Arg 5 10 15	585
ccg acg ccc acc gca ggc ctt aca gtc ttc tct gga cgc tcc ctt gca Pro Thr Pro Thr Ala Gly Leu Thr Val Phe Ser Gly Arg Ser Leu Ala 20 25 30	633

gat gca ccg tgg cct ggc ggc gag ccc ccg gtc acc ttc ctc cgc acg

Asp 35	Ala	Pro	Trp	Pro	Gly 40	Gly	Glu	Pro	Pro	Val 45	Thr	Phe	Leu	Arg	Thr 50	
			ccg Pro													729
_	_		aac Asn 70	_	_			_	_	_	_	_	_			777
_	_		gcc Ala			_			_			-			_	825
			gag Glu													873
_	_		cac His		_				_					_	_	921
ctc Leu	_	taa *	agco	ccgg	gcac	ccg	ccc a	agcco	gggct	g gg	gccct	ccct	geo	cacac	ctag	977
ctto	ccaç	igg c	ctgcc	cccc	ga ca	aggct	ggct	cto	cagto	gag	gcca	ıgaga	atc t	ggaa	atcggg	1037
gtca	gegg	igg c	ctaca	igtco	ct to	ccago	gggct	cto	gggg	cagc	tccc	cagco	ctc t	tccc	catgct	1097
ggtg	gcca	acc g	gtgto	ccctt	g ct	gegg	gatga	ato	ettec	agt	ctct	ccto	ccg t	ctto	cagtg	1157
gccg	gctct	ct t	tata	agaa	ac co	ctggt	catt	gaa	attta	agg	ccca	ıccc	caa g	gtcca	igaatg	1217
acct	caca	aa a	accct	taac	et da	aaaa	aaaa	ı aaa	aa							1251

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<211> 1566

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<220>

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gaggaataaa gaagtcacct ccccagctgt catcatcttc cagcagattg agcaagaata 180
ttttgagcac tacaggaaag acagtccatc aaacccgaga tgatgatcag ccacgtgatt 240

ttttcaagaa gag	gaatagg gtgaa	atgaat ctcatca	agaa aagcagcaat	atg aat 296 Met Asn 1
		~ ~	tca aag aat tct Ser Lys Asn Ser 15	
		Val Pro His	gct tct tcc cag Ala Ser Ser Gln 30	
		-	gaa gaa aaa ctt Glu Glu Lys Leu 45	~
-			aat cca ctc ggt Asn Pro Leu Gly	
0 0000	a Ser Gly Ası	J	ctt gat ttt cag Leu Asp Phe Gln 80	•
			agt gca agt gat Ser Ala Ser Asp 95	
		e Pro Pro Ser	ccc ctc aca cct Pro Leu Thr Pro 110	•
-		-	gtt tac ttt gat Val Tyr Phe Asp 125	
		_	tat tat cct aat Tyr Tyr Pro Asn	
	e Ser Ser Tr		gat atg gcc ctg Asp Met Ala Leu 160	
			cga gtg gga gga Arg Val Gly Gly 175	
		ı Ile Gln Leu	gag tgg ctg caa Glu Trp Leu Gln 190	
			aaa gca agg ccc Lys Ala Arg Pro 205	

gcc cct ggg acc tca ggg gca ctg aaa agc cct ggg aga agt aag cta Ala Pro Gly Thr Ser Gly Ala Leu Lys Ser Pro Gly Arg Ser Lys Leu 215 220 225	968
att gct agt gct ctg tcc aag cca cta cct cac cag gaa ggg gct tca Ile Ala Ser Ala Leu Ser Lys Pro Leu Pro His Gln Glu Gly Ala Ser 230 235 240	1016
aag tca ggc cct tcc cga aag aaa gct ttt cac cat gaa gaa atc cac Lys Ser Gly Pro Ser Arg Lys Lys Ala Phe His His Glu Glu Ile His 245 250 255	1064
cca tca cat tat gca ttt gag act tcc cct aga ccc att gat gtg ctt Pro Ser His Tyr Ala Phe Glu Thr Ser Pro Arg Pro Ile Asp Val Leu 260 265 270	1112
ggt ggt acc agg ttt tgt tct cag agg caa acc ctt gaa atg agg aca Gly Gly Thr Arg Phe Cys Ser Gln Arg Gln Thr Leu Glu Met Arg Thr 275 280 285 290	1160
gaa gaa aaa aaa aaa tca agt aag agt acg aag ctg cag cgc tgg Glu Glu Lys Lys Lys Ser Ser Lys Ser Thr Lys Leu Gln Arg Trp 295 300 305	1208
gat ctg tcc ggc agt gga agc agc tct aag gtg gaa acc agc ggt cac Asp Leu Ser Gly Ser Gly Ser Ser Ser Lys Val Glu Thr Ser Gly His 310 315 320	1256
att cga gtt ccc aaa cag gca gct gtg att ctg gac tca gca gat tcc Ile Arg Val Pro Lys Gln Ala Ala Val Ile Leu Asp Ser Ala Asp Ser 325 330 335	1304
tgt aag gcc tcc aaa aca caa gca cat gca cat cct agg aaa aag gga Cys Lys Ala Ser Lys Thr Gln Ala His Ala His Pro Arg Lys Lys Gly 340 345 350	1352
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aaa aca aac gga gta aag caa aac aca tat aaa cta aaa taa atatcta Lys Thr Asn Gly Val Lys Gln Asn Thr Tyr Lys Leu Lys * 375 380	1449
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														gaa Glu		204
														ctc Leu 60		252
		-	-		-		_					-		cac His		300
														aaa Lys		348
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														aga Arg		444
														ggt Gly 140		492
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		-					-	-				_		gtt Val	-	684

	tcc Ser						_						_	_		732
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_	atg Met	_		-	-		-	-	_				_	-		828
	cct Pro 255															876
	Gly															924
	cac His	-			_					-	-			-		972
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	tgg Trp				_			_	_		_	_	_			1068
	ttc Phe 335				-					-	_			_		1116
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	cca Pro		_	_		-				-		-				1260
	ttt Phe															1308
	gta Val 415		-						-							1356

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					gga Gly										-	1596
					gga Gly 515											1644
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Arg	Arg 655	Leu	Val	Cys	Leu	Thr 660	Leu	Ala	Thr	Asp	Asp 665	Val	Asp	Pro	Glu	
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140 145 150

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					gca Ala											1181
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					cta Leu											1277
					ctt Leu	_				_	_		_		-	1325
_	-	_		_	tcc Ser				_	_			_			1373
-	_	-	_		gca Ala	_		_	_			~				1421
					gac Asp 270									-		1469
					aaa Lys											1517
					tta Leu											1565
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					tca Ser											1661
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	_					gga Gly	-									2	093
						aat Asn 495										2	141
			_			cac His		_		-	_	_	_		-	2	189
					_	tgt Cys			-	-	-		-	_	_	2	237
		-	-		_	gga Gly		_	-	_	-	_	_	-	-	2	285
_	-	-			_	cca Pro	_	_	-		_		-		_	2	333
						att Ile 575		tga *	caca	ıt gt	gaag	gaggo	ato	gtgg	gact	2	385
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					ctg Leu 50											193
					gtc Val											241
					gaa Glu											289
					ttc Phe											337
					ccc Pro											385
_					cac His 130	_	_	_	_	_	_		_	_	_	433
					aac Asn								tga *	ggag	ggtt	482
gggg	gctga	agt g	gctgg	gacat	to to	gagta	cttco	c tta	attaa	acct	tgaa	atcct	ca t	taaa	aggttt	542
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gca agg tca ctt ttc aat agg atg gac ttt gaa gac ttg ggg ttg gta Ala Arg Ser Leu Phe Asn Arg Met Asp Phe Glu Asp Leu Gly Leu Val 30 35 40	146
gta gat tgg gac cac cac ctg cct cca cca gct gcc aag act gtg gtt Val Asp Trp Asp His His Leu Pro Pro Pro Ala Ala Lys Thr Val Val 45 50 55	194
gag aac ctc ccc agg aca gtc atc aga ggc tct cag gct gct ctc acc Glu Asn Leu Pro Arg Thr Val Ile Arg Gly Ser Gln Ala Ala Leu Thr 60 65 70 75	242
gtg ccc tgg gcc cag tac tca agc ttc ttt ctg ttc atg gac tgc tgg Val Pro Trp Ala Gln Tyr Ser Ser Phe Phe Leu Phe Met Asp Cys Trp 80 85 90	290
ggg atg gaa gaa gag tgg cag ttg gga gca ggg gag ggt ggt tat cag Gly Met Glu Glu Glu Trp Gln Leu Gly Ala Gly Glu Gly Gly Tyr Gln 95 100 105	338
ctt atg aag atc aga cca agg cta gaa cac tac tct act ttt ctc aga Leu Met Lys Ile Arg Pro Arg Leu Glu His Tyr Ser Thr Phe Leu Arg 110 115 120	386
caa att cct gtc cct tgt gcc gct atg agc tgc cca ctg atg acg aca Gln Ile Pro Val Pro Cys Ala Ala Met Ser Cys Pro Leu Met Thr Thr 125 130 135	434
ctt atg agg agc aca gac gag ata agg ctc gaa aac agc agc agc aac Leu Met Arg Ser Thr Asp Glu Ile Arg Leu Glu Asn Ser Ser Ser Asn 140 145 150 155	482
acc gac tgg aga acc tcc atg gag cca tgt aca cgt gag gag gtt ggg Thr Asp Trp Arg Thr Ser Met Glu Pro Cys Thr Arg Glu Glu Val Gly 160 165 170	530
gct gag tgc tgg ccc tct gcg tct tcc tta tta acc ttg aat cct cat Ala Glu Cys Trp Pro Ser Ala Ser Ser Leu Leu Thr Leu Asn Pro His	578

175 180 185

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609

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aag aac tgg ctc aag aaa ttt gcc tcg aaa acc aaa aaa aag gtt tgg Lys Asn Trp Leu Lys Lys Phe Ala Ser Lys Thr Lys Lys Lys Val Trp 45 50 55	196
tat gaa agt cct tcc ttg ggt tct cac tcg act tac aaa cca tcc aag Tyr Glu Ser Pro Ser Leu Gly Ser His Ser Thr Tyr Lys Pro Ser Lys 60 65 70	244
ttg gaa ttc ctc atg agg agc acc tca aag aaa acc agg aag gaa gac Leu Glu Phe Leu Met Arg Ser Thr Ser Lys Lys Thr Arg Lys Glu Asp 75 80 85	292
cat gcg cgc ctg agg gcc ctg aac ggc ctc ctc tat aag gca ctg aca His Ala Arg Leu Arg Ala Leu Asn Gly Leu Leu Tyr Lys Ala Leu Thr 90 95 100 105	340
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gtg gag ctc tcc aag gtt tcc ctg act cca gac ttc tca gcc tgc cga Val Glu Leu Ser Lys Val Ser Leu Thr Pro Asp Phe Ser Ala Cys Arg 125 130 135	436
gcg tac tgg aag aca acg ctc tct gct gag cag aac gca cac atg gag	484

Ala Tyr S	Trp Lys 140	Thr Thr	Leu	Ser 145	Ala	Glu	Gln	Asn	Ala 150	His	Met	Glu	
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cag cag a Gln Gln 7 170			. Val										580
gga aat g Gly Asn A		_			_	_		_	_	_	-	-	628
ttt gga o			_	_			_			_			676
gac cct g Asp Pro A				_					-			•	724
tcc agt o Ser Ser I 235												_	772
gag tac a Glu Tyr I 250													820
ggg cag g Gly Gln V													868
gcc aag c Ala Lys F	_		_	_	_			_	_		_		916
ggc gag g Gly Glu G													964
gaa tgc t Glu Cys T 315													1012
ggc aga a Gly Arg T 330											tag *	atg	1060
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gtc aac ctc att gcc tgc ctg gcc tgg tgg atc ggc gga ggc tcg ggg Val Asn Leu Ile Ala Cys Leu Ala Trp Trp Ile Gly Gly Gly Ser Gly 55 60 65	306
acc aac ttc ggc ctg gcc ttc gtg tgg ctg ctc ctg ttc acg cct tgc Thr Asn Phe Gly Leu Ala Phe Val Trp Leu Leu Phe Thr Pro Cys 70 75 80	354
ggc tac gtg tgc tgg ttc cgg cct gtc tac aag gcc ttc cga gcc gac Gly Tyr Val Cys Trp Phe Arg Pro Val Tyr Lys Ala Phe Arg Ala Asp 85 90 95 100	402
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ggc tgg ctg tcg gca att gga ttc ttc cag tac agc ccg ggc gct gcc Gly Trp Leu Ser Ala Ile Gly Phe Phe Gln Tyr Ser Pro Gly Ala Ala 135 140 145	546

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atg gcc atc gcg atc atg aag gtg cac agg atc tac cga ggg ggc tgg Met Ala Ile Ala Ile Met Lys Val His Arg Ile Tyr Arg Gly Gly Trp 165 170 175 180	642
cgg aag ctt cca gaa ggc cag acg gag tgg cac acg ggc ctt ggc gga Arg Lys Leu Pro Glu Gly Gln Thr Glu Trp His Thr Gly Leu Gly Gly 185 190 195	690
acc ccc cgc gac ggg ggc ccc gtc aac atc ttt cgg cga agc ttg ccc Thr Pro Arg Asp Gly Gly Pro Val Asn Ile Phe Arg Arg Ser Leu Pro 200 205 210	738
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30 35 40	
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	cag Gln			_			_		_			_	_	_	_	459
	agg Arg		_		-		-		-	_	-				_	507
	gtt Val 125		-	-		-	-		-	-	_					555
	gct Ala															603
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	aac Asn															699
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	gtt Val	-		_	-			-								891
	ttt Phe															939
	ttg Leu			_				-	_							987
	gga Gly 285															1035

			gag Glu													1083
			cgg Arg					-	-	_	-		-	-		1131
			cag Gln 335													1179
	-		gag Glu	_	-	-	_	_			_	_			-	1227
	_	_	ctg Leu	-		_			_			_		_	-	1275
		_	ctg Leu		_	-	_	_	_		_					1323
			act Thr	-	_				_		_			_		1371
			aca Thr 415													1419
		-	acc Thr		_						-					1467
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			cct Pro													1563
			ttt Phe													1611
			gcc Ala 495													1659
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					tgg Trp											1899
					cgg Arg											1947
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					atc Ile 625											2043
					ctg Leu											2091
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					gat Asp										_	2187
					tgt Cys											2235
					cag Gln 705											2283
					atg Met											2331
					tta Leu											2379
					aag Lys											2427

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		aag aat Lys Asn										2475
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		aga aaa Arg Lys 800										2571
		aaa gac Lys Asp										2619
		gtg gag Val Glu		r Pro						_	_	2667
	-	cac ata His Ile		_	_		-	-				2715
		gga cag Gly Gln 865										2763
		cac gca His Ala 880										2811
	_	ccc acc Pro Thr	_	_	_	-			_	_	_	2859
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		gaa cag Glu Gln										2955
		ggc gag Gly Glu 945										3003
		gcc atc Ala Ile 960										3051
		agt gtt Ser Val										3099

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tca to Ser Se															241
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					gtc Val											1201
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						gac Asp										1441
		_		-		gag Glu 405	-	-	-		-					1489
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	_					aat Asn	_		_	_		_	_		_	1585
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		_			-	cag Gln	_			-	_					1681
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						cac His										1921
						gag Glu										1969

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					cac His										2881
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			_		ctg Leu					-			_		3121
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					gtc Val 980										3217
-					cca Pro	-		Ser			_		Pro		3265
_		Leu	~ ~		ctt Leu		Glu				_	Leu		_	3313

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tcc cag gca cct ggc cat ccc tgg ggc cca gtc acc acc tac tgc cac Ser Gln Ala Pro Gly His Pro Trp Gly Pro Val Thr Thr Tyr Cys His 1040 1045 1050	3409
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ctc tta gat tct aca gag ctg gat att gag gat ttc tga caggactctg Leu Leu Asp Ser Thr Glu Leu Asp Ile Glu Asp Phe * 1215 1220 1225	3938
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					ttt Phe										772
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_	_				cga Arg	_		_	_		-	-		_	1012
-					gat Asp										1060
	_	-	_		ctg Leu 350	_	_	_							1108

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cat cat gaa tta att gaa tat gtt ata gct aaa gga aaa ctc atc tat His His Glu Leu Ile Glu Tyr Val Ile Ala Lys Gly Lys Leu Ile Tyr 410 415 420	1300
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15 20

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					ata Ile											576
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					tgc Cys											672
					gaa Glu								-			720
_			-	_	cag Gln		_					_		_		768
					gaa Glu											816
				_	gcc Ala 195				-	_	_			_	_	864
		-		_	gaa Glu		-			_	_	-	-			912
					gag Glu											960
	_			_	aat Asn	_	_	-	-	-		_	-	-		1008
cgt	gac	acg	tat	gat	gct	gtt	tta	tgg	cta	aga	aat	aac	aga	gac	aaa	1056

Arg	Asp 255	Thr	Tyr	Asp	Ala	Val 260	Leu	Trp	Leu	Arg	Asn 265	Asn	Arg	Asp	Lys		
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-				_				gaa Glu							_	11	152
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cct ctc gct tct ttt cga cca cca ttt tgg ggg ctg agg cac tca cgg Pro Leu Ala Ser Phe Arg Pro Pro Phe Trp Gly Leu Arg His Ser Arg 5 10 15 20	162												
ggc ctc ccc agg ttt cac tcc gtt tct aca cag tcg gag ccc cat gga Gly Leu Pro Arg Phe His Ser Val Ser Thr Gln Ser Glu Pro His Gly 25 30 35	210												
tct ccc atc tcc cgg agg aac cgt gaa gcc aaa cag aag cgc ctg cga Ser Pro Ile Ser Arg Arg Asn Arg Glu Ala Lys Gln Lys Arg Leu Arg 40 45 50	258												
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cct gca gaa tcc att aag gcc tgg agg cct aag gag tta gta ttg tat Pro Ala Glu Ser Ile Lys Ala Trp Arg Pro Lys Glu Leu Val Leu Tyr 70 75 80	354												
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		aac Asn						2370
		tcg Ser						2418
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		cag Gln						2610
		gtg Val						2658
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_	-	_	_		act Thr									_	-	1118
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		aaa Lys														2	249
		gct Ala														2	297
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		gag Glu 100														3	393
		atc Ile				_		-	_		-					2	141
		atg Met														Ž.	189
_	-	gag Glu														ŗ	537
		ctc Leu		_		-			_	-						Ĭ.	585
_		ctc Leu 180	_	_	_		_			_						•	633
~	_	cag Gln		_	_	_	-									6	581
		gtg Val														•	729
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qtatttctta aatqtatttq attgatqcct cattcctccc taaaatgtat aaaaccaagc 2886 2946 tgtacctcga ccaccttggg cacatgttcc caggccctcc tgaggtctgt gtcacgggcc 3003 atggccactc atatttggct cagaataaat ctcttcaaat attttaaaaa aaaaaaa <210> 38 <211> 631 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (68)..(466) <400> 38 gatecgaatt egeggeegeg tegacteact gagaaceate eeggtaacee gateaeeget 60 ggtcacc atg aac cac att gtg caa acc ttc tct cct gtc aac agc ggc 109 Met Asn His Ile Val Gln Thr Phe Ser Pro Val Asn Ser Gly 1 5 157 cag cct ccc aac tac gag atg ctc aag gag gag cag gaa gtg gct atg Gln Pro Pro Asn Tyr Glu Met Leu Lys Glu Glu Glu Glu Val Ala Met 20 ctg ggg gtg ccc cac aac cct gct ccc ccg atg tcc acc gtg atc cac 205 Leu Gly Val Pro His Asn Pro Ala Pro Pro Met Ser Thr Val Ile His 253 atc cgc agc gag acc tcc gtg cct gac cat gtg gtc tgg tcc ctg ttc Ile Arg Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe 50 55 301 aac acc ctc ttc atg aac acc tgc tgc ctg ggc ttc ata gca ttc gcg Asn Thr Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala 65 70 tac tcc gtg aag tct agg gac agg aag atg gtt ggc gac gtg acc ggg 349 Tyr Ser Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly 80 85 397 gcc cag gcc tat gcc tcc acc gcc aag tgc ctg aac atc tgg gcc ctg Ala Gln Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu 95 100 445 att ttg ggc atc ttc atg acc att ctg ctc atc atc cca gtg ttg Ile Leu Gly Ile Phe Met Thr Ile Leu Leu Ile Ile Pro Val Leu 115 120

gtc gtc cag gcc cag cga tag at caggaggcat cattgaggcc aggagctctg

Val Val Gln Ala Gln Arg * 130

498

558 cccqtqaqct qtatccacqt actctatctt ccattcttcg cctgccccca gaggccagag ctctgccctt gactgtattc acttattcag ctccattctg cctgtccaaa gcgagtctga 618 631 ttagccttta caa <210> 39 <211> 2995 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (274)..(2271) <400> 39 ggagcaggaa acccggcgca gccgggcgca ttgggccgcg atgcaacagc agcagcagga 60 120 cgccgccgcc actgaggaag aagccggccc agccgccgcc gcgtccggac cctcgcgcct 180 ggatcccagc gccccgatcc cggcgcccca acccccacgc ccgcctccgc caactttcac 240 gctgcctcgg cggcccggcc cggctcgacg cca atg gtg gag gcc ata gtg gag 294 Met Val Glu Ala Ile Val Glu ttt gac tac cag gcc cag cac gat gat gag ctg acg atc agc gtg ggt 342 Phe Asp Tyr Gln Ala Gln His Asp Asp Glu Leu Thr Ile Ser Val Gly 15 10 390 gaa atc atc acc aac atc agg aag gag gat gga ggc tgg tgg gag gga Glu Ile Ile Thr Asn Ile Arg Lys Glu Asp Gly Gly Trp Trp Glu Gly 30 25 cag atc aac ggc agg aga ggt ttg ttc cct gac aac ttt gta aga gaa 438 Gln Ile Asn Gly Arg Arg Gly Leu Phe Pro Asp Asn Phe Val Arg Glu 40 45 50 55 ata aag aaa gag atg aag aaa gac cct ctc acc aac aaa gct cca gaa 486 Ile Lys Lys Glu Met Lys Lys Asp Pro Leu Thr Asn Lys Ala Pro Glu 70 60 65 534 aag ccc ctg cac gaa gtg ccc agt gga aac tct ttg ctg tct tct gaa Lys Pro Leu His Glu Val Pro Ser Gly Asn Ser Leu Leu Ser Ser Glu 85 75 80 582 acg att tta aga acc aat aag aga ggc gag cga cgg agg cgc cgg tgc Thr Ile Leu Arg Thr Asn Lys Arg Gly Glu Arg Arg Arg Arg Cys 95

cag gtg gca ttc agc tac ctg ccc cag aat gac gat gaa ctt gag ctg

630

Gln	Val 105	Ala	Phe	Ser	Tyr	Leu 110	Pro	Gln	Asn	Asp	Asp 115	Glu	Leu	Glu	Leu	
								gta Val								678
								act Thr								726
	-		_				_	gat Asp 160						-	_	774
								agg Arg								822
~	~~~		~		_	_		aag Lys		~	~ ~	~				870
	_		_	_		_		aag Lys		_	_					918
	_				_	_		atc Ile			_					966
								gta Val 240								1014
		_			_			gac Asp					_	_	_	1062
_			_	_	_	_		tgc Cys		-						1110
_	_		-	_	-	-		atc Ile		_		_		_		1158
			_	-	_		-	gta Val				_			_	1206
		_	_					gat Asp 320				_				1254
_	_		_	_	-			aga Arg		_	_		_			1302

330	335	340	
		c act gag aga aaa c Thr Glu Arg Lys 355	
		a atg ctt cca aac 1 Met Leu Pro Asr)	
		a aaa ctg gat tta b Lys Leu Asp Leu 390	Gln
Lys Pro Ser V		g cct cgg cca cct s Pro Arg Pro Pro 405	
		c ccg aga agg ccg o Pro Arg Arg Pro 420	_
		gac agt cca aag Asp Ser Pro Lys 435	_
		g gac aaa gat cto 1 Asp Lys Asp Leu)	
		gac tcc gtg gta Asp Ser Val Val 470	Ser
Ser Thr Glu I		c aga cca aaa gct c Arg Pro Lys Ala 485	
		t tca tcc ctt tca Ser Ser Leu Ser 500	
		g gat aag gag gaa 1 Asp Lys Glu Glu 515	
		a aag aaa act tco r Lys Lys Thr Ser)	
		a gca tcc ctg ccg s Ala Ser Leu Pro 550	Pro
Lys Pro Gly T		g cca gcc cct ctg y Pro Ala Pro Lei 565	

2022 tca gcg gcg ccc tcc ccc ctg tca tcc tct ttg gga aca gct gga cac Ser Ala Ala Pro Ser Pro Leu Ser Ser Ser Leu Gly Thr Ala Gly His 575 570 2070 aga qcc aac tcc ccg tct ctg ttc ggc acg gaa gga aaa cca aag atg Arg Ala Asn Ser Pro Ser Leu Phe Gly Thr Glu Gly Lys Pro Lys Met 590 585 gag cct gcg gcc agc agc cag gcg gcc gtg gag gag cta agg aca cag 2118 Glu Pro Ala Ala Ser Ser Gln Ala Ala Val Glu Glu Leu Arg Thr Gln 610 615 605 600 2166 gtc cgc gag ctg agg agc atc atc gag acc atg aag gac cag cag aaa Val Arg Glu Leu Arg Ser Ile Ile Glu Thr Met Lys Asp Gln Gln Lys 2214 cga gag att aaa cag tta ttg tct gag ttg gat gaa gag aag aaa atc Arg Glu Ile Lys Gln Leu Leu Ser Glu Leu Asp Glu Glu Lys Lys Ile 635 2262 cgg ctt cgg ttg cag atg gaa gtg aac gac ata aag aaa gct cta caa Arg Leu Arg Leu Gln Met Glu Val Asn Asp Ile Lys Lys Ala Leu Gln 655 650 tca aaa tga atacttg atcaatgaaa tgtcacatta ttcatcctga gtccgagact 2318 Ser Lys 665 caaattttct gccccagcca aaataatctt gtgccaaaag attaaaggtt tgcctcaaaa 2378 tgtccctgtt tgaaagatta gcacaaaagt cttgatagca caacacaaat tccatccaag 2438 aggagaatct tccccagggt ttagtcctgg ggctggcact cgttgtgact tacacagagc 2498 2558 aaaattgtgc taaaqqcttt tctactctga gatctcaatg cgaaatgaaa actcaggcag tttagtccat agtggtacta ttttgatgat attttccatt aataaaatgt aatttcagat 2618 2678 tattcgttta caagctttat aattttatga ttttttaatc gtgttttgtc acagacttcc 2738 ctagtgtttg tactacacgt agtcagaagc gagtgtcctt ttcttttgct tcaggctaag 2798 agctgcctcg ctctttgtcc ccccattagg attctattac atatgcaatt gtaggttcaa cctgtccctt tccctgccag caaaccccac caccctaaga gaaattttag cttatatatg 2858 2918 acggtatatt tacaaaaaga gaaagagaaa atctggtatt tgcaatgatc tgtgccttct 2978 ttttaccacc ctcttgattg gagcttttgt gatgcagcta ccatgattca aaaaaattaa 2995 aaattaaaaa aaaaaaa

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	aag Lys															774
	cag Gln															822
	ggg Gly 185															870
	gca Ala															918
	gac Asp															966
_	gta Val	-														1014
	cct Pro												_			1062
	agg Arg 265															1110
	cag Gln															1158
	atc Ile		_	_	_		_	_				-				1206
	ggc Gly	_	_	~ ~				-				_				1254
	gac Asp															1302
	gct Ala 345		_					_					_			1350
	att Ile															1398
aca	gaa	gaa	aaa	gaa	aga	cca	gag	aga	gag	cca	aaa	ctg	gat	tta	cag	1446

Thr	Glu	Clu	Tare	G111	Δrα	Pro	G111	Δrα	Glu	Pro	Lvs	Len	Asp	Leu	Gln	
1111	Giu	Giu	шys	380	111.9	110	OIU	111.9	385	110	<i>1</i>	200	1100	390	02	
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														ccg Pro		1542
														aag Lys	_	1590
														ctc Leu		1638
														gta Val 470		1686
														gct Ala		1734
														aac Asn		1782
														ggt Gly		1830
														tct Ser		1878
														acg Thr 550		1926
														gtg Val		1974
														acc Thr		2022
														ttg Leu		2070
														gac Asp		2118

600	60)5	610		615	
	t cta caa to a Leu Gln Se 620		atacttgatc	aatgaaatgt	cacattattc	2172
atcctgagtc	cgagactcaa	attttctgcc	ccagccaaaa	taatcttgtg	ccaaaagatt	2232
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cagagacaca	gcaagatgcc	cagggagtgc	cgcttcctgg	gctagagaca	agcaccagcc	240
tgcagtggag	aacgcaggac	cccgctgccc	agaaggagca	gccacggcct	gcggaggact	300
ggcccagcaa	ggtcccaggt	cttccctctc	ctcagcgcct	aagagagagg	cccagtgcgg	360

gtgaggagtc gcgaggaaga ggcggaaggc gccggaaggc acc atg ttc cgc aag

415

Met Phe Arg Lys

	aag Lys									463
	cac His									511
	caa Gln		-		_	_				559
	gac Asp 55									607
	gtg Val									655
	aac Asn									703
	cgc Arg									751
	gat Asp									799
_	tct Ser 135		-							847
	aca Thr	Pro	Ala	His	Lys					895
	cgg Arg									943
	gcc Ala									991
	ctg Leu									1039
	cat His 215									1087

				gtg Val								13	135
				aag Lys 250								1:	183
		 _		ctg Leu		_	_	_		-		1:	231
				cca Pro								1:	279
				aac Asn								1:	327
				ccg Pro						_		1:	375
				cag Gln 330								1.	423
				tct Ser								1.	471
_	_			agc Ser							_	1	519
-	_	 -	_	gct Ala								1!	567
				ctc Leu								1	615
				tac Tyr 410								1	663
				gag Glu								1	711
				aag Lys								1	759

gtg Val	gtg Val	atc Ile 455	atg Met	cgg Arg	gac Asp	tac Tyr	cag Gln 460	cac His	ttc Phe	aac Asn	gtg Val	gtg Val 465	gag Glu	atg Met	tac Tyr	1807
													gag Glu			1855
													ctg Leu			1903
													ctg Leu			1951
													gac Asp 530			1999
													gga Gly			2047
													gtg Val			2095
													tat Tyr			2143
													atg Met			2191
	-												atg Met 610			2239
													aag Lys			2287
													gac Asp			2335
													ctg Leu			2383
aca Thr	ggg	cta Leu	cct Pro	gag Glu 665	tgc Cys	ctg Leu	gtg Val	ccc Pro	ctg Leu 670	atc Ile	cag Gln	ctc Leu	tac Tyr	cga Arg 675	aag Lys	2431
cag	acc	tcc	acc	tgc	tga	gcc	cac (cccaa	agta	tg c	ctgc	cacc	t ac	gccc	acag	2485

Gln Thr Ser Thr Cys * 680

	gcagggcaca	ctgggcagcc	agcctgccgg	caggacttgc	ctgcctcctc	ctctcagtat	2545
	tctctccaaa	gattgaaatg	tgaagcccca	gccccaccct	ctgcccttca	gcctactggg	2605
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	cggaatcccg	cttcctccct	cacgtctgat	gtcctgaagg	tgcagtccca	cctgtacagc	2965
,	ccctccccgc	ccagaactgt	gaatggcctg	ctccaggcca	tggctggggg	cagggagtga	3025
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<211> 1968

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (154)..(1968)

<400> 42

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ggtgacaggc gttgagacca ccgaagggaa ccc atg gct agg atc agt ttt tcc Met Ala Arg Ile Ser Phe Ser 1 5

tac ctc tgc cca gcc tcc tgg tac ttc act gtg ccc aca gtg agt cca
Tyr Leu Cys Pro Ala Ser Trp Tyr Phe Thr Val Pro Thr Val Ser Pro 10 15 20

ttt ctc cgt cag cgg gtg gca ttc ctg gga ctc ttc ttc ata tcc tgt
Phe Leu Arg Gln Arg Val Ala Phe Leu Gly Leu Phe Phe Ile Ser Cys
25 30 35

ctc ctt tta ctt atg tta atc ata gac ttt cga cat tgg agt gct tca 318
Leu Leu Leu Met Leu Ile Ile Asp Phe Arg His Trp Ser Ala Ser
40 45 50 55

cca Pro										366
gaa Glu		-	_	-		_			_	414
 gac Asp							_			462
cat His 105										510
cgc Arg										558
atg Met								-	_	606
agc Ser										654
ctt Leu										702
cag Gln 185										750
gac Asp										798
 gaa Glu										846
gac Asp										894
gga Gly										942
caa Gln 265										990

	cag Gln															1038
	gat Asp					_					_		_			1086
	ctg Leu															1134
	ctg Leu															1182
	ctg Leu 345															1230
	aca Thr							_		_			_	_		1278
	gga Gly															1326
	tcc Ser															1374
	gac Asp															1422
	aca Thr 425															1470
	gcc Ala															1518
	cag Gln															1566
	ctc Leu															1614
	gaa Glu															1662
cag	ctg	gtg	tat	gac	cga	gag	gtt	cag	tgg	acg	ctg	gga	gcc	att	cta	1710

Gln Leu Val Tyr Asp Arg Glu Val Gln Trp Thr Leu Gly Ala Ile Leu 505 510 515	
tat aaa aca cga ttc tta cca ctc agg gat ctt cgg cag gaa ggt gtc Tyr Lys Thr Arg Phe Leu Pro Leu Arg Asp Leu Arg Gln Glu Gly Val 520 535	1758
cga caa gcc cat ggt agc tgg ttc cgt ctc tcc ttt gta tac aac cac Arg Gln Ala His Gly Ser Trp Phe Arg Leu Ser Phe Val Tyr Asn His 540 545 550	1806
tat ctc ttc ttt gcc tgt atc ctg gtg gtg cta ctg gcc atc ttc cta Tyr Leu Phe Phe Ala Cys Ile Leu Val Val Leu Leu Ala Ile Phe Leu 555 560 565	1854
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gct cca ttg gac ttg ctg tgg ctt gaa gag gtg gtg ccc atg atg gga Ala Pro Leu Asp Leu Leu Trp Leu Glu Glu Val Val Pro Met Met Gly 585 590 595	1950
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actggttgat tcatatggag gtcagagtgg aagcaggtgt gagagggtcc cacagaagaa	240
aacatggcag ccaaagtgtt tgagtccacg gtaagtttgg cttggcctta gctgttgcag	300
gagacctgtg aactctgcct tatataatgt ggatgttggg cacagagctg tcatctttga	360
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cca atc atc act ggt agc aaa gat tta cag aat gtc aat atc aca ctg Pro Ile Ile Thr Gly Ser Lys Asp Leu Gln Asn Val Asn Ile Thr Leu 20 25 30	513
cgc atc atc ttc cag cct gtt gct agc cag ctt cct cgc atc ttc acc Arg Ile Ile Phe Gln Pro Val Ala Ser Gln Leu Pro Arg Ile Phe Thr 35 40 45	561
agc atc gga gag gac tat gat gag cct gtg ctg acg tac atc acg acc Ser Ile Gly Glu Asp Tyr Asp Glu Pro Val Leu Thr Tyr Ile Thr Thr 50 55 60	609
gag atc ctc aag tca gtg gtg gct cgc ttt gat gct gga gaa gtt atc Glu Ile Leu Lys Ser Val Val Ala Arg Phe Asp Ala Gly Glu Val Ile 65 70 75 80	657
act cag aga gag ctg gtc tcc agg cag gtg agc aac gac ctt acg gag Thr Gln Arg Glu Leu Val Ser Arg Gln Val Ser Asn Asp Leu Thr Glu 85 90 95	705
caa gca gcc aca ttt ggg ctc atc ctg gac gac gtg tcc ttg aca tat Gln Ala Ala Thr Phe Gly Leu Ile Leu Asp Asp Val Ser Leu Thr Tyr 100 105 110	753
ctg acc ttt gga aag gag ttc aca gaa gca gtg gaa gcc aaa cag gtg Leu Thr Phe Gly Lys Glu Phe Thr Glu Ala Val Glu Ala Lys Gln Val 115 120 125	801
gct cag cag gaa gca gag agg gcc aga ttt gtg aag gaa aag gct gag Ala Gln Gln Glu Ala Glu Arg Ala Arg Phe Val Lys Glu Lys Ala Glu 130 135 140	849
cag cag aaa aag gct gag cag cag aaa aag gtt gag cag cag aaa aag Gln Gln Lys Lys Ala Glu Gln Gln Lys Lys Val Glu Gln Gln Lys Lys 145 150 155 160	897
gca gcc gtg atc tct gct gag ggc gac tcc aag gca acc gag ctg att Ala Ala Val Ile Ser Ala Glu Gly Asp Ser Lys Ala Thr Glu Leu Ile 165 170 175	945
gcc aac tca ctg gcc acc gcg ggg gac ggc ctg atg gag ctg tgc aag Ala Asn Ser Leu Ala Thr Ala Gly Asp Gly Leu Met Glu Leu Cys Lys 180 185 190	993
ttg gaa gcc gcg gag gct ctc gga aca tga c ctacctgccg gcggggcagt Leu Glu Ala Ala Glu Ala Leu Gly Thr * 195 200	1044
ccgctcctcc ggctgcccca tgagggccca ccctgcctgc acctccgcag gctgactggg	1104
ccacagcccc aatgattctt aacactgcct taccccccta ccccagaaat cactgaaatt	1164
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aaaaa	1229

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				act Thr												159
				aca Thr												207
			-	tat Tyr 45				_		_	_			_		255
		-	_	gga Gly			_	_					_			303
				gtt Val												351
				caa Gln												399
_	_	_	_	gac Asp	-	-	-				_				_	447
		_		tta Leu 125		_	_		_	_		_	_			495
_		_	_	gcc Ala			_	_	_					_		543
				ggg Gly												591

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			ctt Leu 50													371
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			aga Arg													467
			tta Leu	-	-		_	-						_	_	515
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		_	atg Met 130	_			_	_					_			611
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cac tac cag tac aag agc atc cct gtg gag gac aac cac aag gca gac His Tyr Gln Tyr Lys Ser Ile Pro Val Glu Asp Asn His Lys Ala Asp 220 225 230	964
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_		•	~			cct Pro		•	_		~			-	_	579
						gag Glu 110										627
	-			-	-	cct Pro		-	-	_					_	675
						gac Asp										723
_		_		_	_	ctc Leu				_			-			771
_	_					agg Arg			-					-		819
-	~ ~	~		_	~	gaa Glu 190	_	_			_	_	_			867
						ctg Leu										915
						aat Asn										963
						tgt Cys										1011
-		_		-		cac His		-			_			_		1059
		-	_		-	gga Gly 270		_			_	_				1107
				-	-	cac His	_		_					_		1155
						agt Ser										1203

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			aga Arg													631
			cta Leu													679
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			tgg Trp 150	_	_					_	_		_		_	775
			aaa Lys		_		-			_			_		_	823
			ttt Phe													871
-		-	atg Met		_	_	_		_				-	-		919
_	_		caa Gln			_						_				967
_	_	_	att Ile 230			-			-		_	_				1015
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	-	-	ttt Phe			_		-	_	_					_	1111
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-	-	-			tta Leu							-			-	130)3
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	ac att aca sn Ile Thr 550						
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	at acc aaa yr Thr Lys						
gct gat ta Ala Asp Ty 595	at gac tgg yr Asp Trp	_		_	Gly Arg		
tat tta at Tyr Leu Me	tg gac ctt et Asp Leu 615						
act cat to		_	-	_		-	_
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cag tgt ga Gln Cys G 675	aa ttg ttt lu Leu Phe				Pro Gly		
gat acc ct Asp Thr Le							
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gct tct aa Ala Ser Ly 72	ys Tyr Leu						
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<212> DNA

<213> Homo sapiens

<220>

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<222> (150)..(2729)

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cggccccgga gcccctcggc ggcgccacc atg tac tcg gga gcc ggc ccc gca Met Tyr Ser Gly Ala Gly Pro Ala

	-				ccg Pro	_							_		-	221
					gac Asp 30											269
_	_				gaa Glu	_	-									317
	-	_	-		aag Lys			_	-	-		_	_			365
_			_		atg Met	-	_					_				413
-		_			ttt Phe	-			-					-	_	461
		_			agg Arg 110	-	_			_		-	_	_		509
	-		_	-	cgc Arg											557
_		_	_	_	gcg Ala			-	-					_		605
					acg Thr											653
_			-		tac Tyr					_						701
	-		_		aac Asn 190						_	-				749
~ ~			_		gtc Val							_	_	_		797
	-	-		-	aca Thr				_	_	_		_			845

		tgt Cys 235														893
	_	aca Thr	-				-	_				_				941
		gtg Val														989
_	_	aat Asn						-	-					_	_	1037
_	_	gag Glu	-		-	-			_	_		-	_			1085
_	-	agg Arg 315		_	_	_	_	_						_		1133
	_	gga Gly	_		_							_		-	-	1181
		gtg Val	-			_	-					_	_		-	1229
		acc Thr	-		-			-		_			-			1277
_		att Ile	_		_	_	-	-	-	-				-		1325
	-	cgt Arg 395	-				_	-		-		_		-		1373
		cgg Arg														1421
	-	att Ile				-	_		_		_	_			_	1469
_		cac His	_					-			-			_		1517
gcc	ccc	cag	cgc	cag	tgc	acg	gaa	gtc	cat	ctg	aag	tcc	ttc	aca	gag	1565

Ala	Pro	Gln	Arg 460	Gln	Cys	Thr	Glu	Val 465	His	Leu	Lys	Ser	Phe 470	Thr	Glu		
_		_	_		tcg Ser	_	_	-		_			_		_	1	1613
					tac Tyr											1	1661
			_	-	aac Asn 510	_				-	-	_				1	1709
	_			_	acg Thr						_	_	_			1	L757
_	~	~ ~	-		atg Met	_	_	_	_		_	_	_			1	L805
~			_		cag Gln		-				-	_	_			1	L853
					gtg Val											1	L901
_			_	_	ccc Pro 590	_			_							1	L949
					ggg Gly											1	L997
					ccc Pro											2	2045
					atc Ile											2	2093
					tac Tyr											2	2141
					ggt Gly 670											2	2189
					gcc Ala											2	237

685 690 695 gac tac cag ccc ggg atc acc ttc atc gtg gtg cag aag agg cac cac 2285 Asp Tyr Gln Pro Gly Ile Thr Phe Ile Val Val Gln Lys Arg His His 705 acc cgg ctc ttc tgc act gac aag aac gag cgg gtt ggg aaa agt gga 2333 Thr Arg Leu Phe Cys Thr Asp Lys Asn Glu Arg Val Gly Lys Ser Gly 720 2381 aac att cca gca ggc acg act gtg gac acg aaa atc acc cac ccc acc Asn Ile Pro Ala Gly Thr Thr Val Asp Thr Lys Ile Thr His Pro Thr 730 735 gag ttc gac ttc tac ctg tgt agt cac gct ggc atc cag ggg aca agc 2429 Glu Phe Asp Phe Tyr Leu Cys Ser His Ala Gly Ile Gln Gly Thr Ser 745 750 2477 agg cct tcg cac tat cac gtc ctc tgg gac gac aat cgt ttc tcc tct Arg Pro Ser His Tyr His Val Leu Trp Asp Asp Asn Arg Phe Ser Ser 775 765 770 gat gag ctg cag atc cta acc tac cag ctg tgt cac acc tac gtg cgc 2525 Asp Glu Leu Gln Ile Leu Thr Tyr Gln Leu Cys His Thr Tyr Val Arg 780 785 2573 tgc aca cgc tcc gtg tcc atc cca gcg cca gca tac tac gct cac ctg Cys Thr Arg Ser Val Ser Ile Pro Ala Pro Ala Tyr Tyr Ala His Leu 795 800 2621 gtg gcc ttc cgg gcc agg tac cac ctg gtg gat aag gaa cat gac agt Val Ala Phe Arg Ala Arg Tyr His Leu Val Asp Lys Glu His Asp Ser 815 2669 gct gaa gga agc cat acc tct ggg cag agt aac ggg cga gac cac caa Ala Glu Gly Ser His Thr Ser Gly Gln Ser Asn Gly Arg Asp His Gln 825 830 835 2717 gca ctg gcc aag gcg gtc cag gtt cac caa gac act ctg cgc acc atg Ala Leu Ala Lys Ala Val Gln Val His Gln Asp Thr Leu Arg Thr Met 845 850 tac ttt gct tga cat gttttagtgt ttagcgattg tgtaccgagt gggattcacg 2772 Tyr Phe Ala 860 agaccageta cacteagace aacagatgge cagecettee gtgacageca geategaaca 2832 2892 tgagacgtca ttgattttat tagattctcc gttttccaga atgccttccg tcccagattt caaacttgga ttttgaactg cagacctgta tgagaaccca atgtcatagg aaatatggtt 2952 tgctaaaatc tataagctgc ttattaaaac agagtcccgt gtgtcctaaa aaaaaaaaa 3011

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ctttcaatgt	catctttgga ggtcaagtta tcagaaatgg ggatgaatct ctgccgtacc	180
tgcctcttca	cctccaccct gatcactact ctcggacaaa gtcaattgca gagcagaagg	240
tgctggaggc	gaatgctaca cccctggaca gaggcgacgg tgtcttaaga acctgcgctc	300
tgaggccagc	tggcatctat gggcctggag aacaaagaca ccttcccagg atagtcagct	360
acatcgagaa	gggtctgttc aagtttgtct acggcgaccc caggagcctg gttgagtttg	420
tccacgtgga	taacttggtg caggeteaca ttetggeete agaageeetg agagetgaca	480
agggccatat	tgcctctggg cagccctact tcatctcaga tggcagaccc gtgaacaact	540
ttgagttctt	ccggcctctg gttgagggcc tgggctacac attcccgtct acccgcctgc	600
cattgacctt	ggtctactgc tttgcttttc taacagag atg gtt cac ttc att Met Val His Phe Ile 1 5	653
	a ctc tac aac ttc cag ccc ttc ctc act cgc act gaa gtt g Leu Tyr Asn Phe Gln Pro Phe Leu Thr Arg Thr Glu Val 10 15 20	701
	t ggt gtc aca cat tat ttt agc tta gag aaa gcc aag aaa r Gly Val Thr His Tyr Phe Ser Leu Glu Lys Ala Lys Lys 25 30 35	749
	t tat aag gct cag cca ttt gac ctc cag gaa gca gtg gaa y Tyr Lys Ala Gln Pro Phe Asp Leu Gln Glu Ala Val Glu 0 45 50	797
	a gcc cat ggt cat ggc aga agt tct gga agt cgt gac tcg s Ala His Gly His Gly Arg Ser Ser Gly Ser Arg Asp Ser 60 65	845
	t gtt tgg gat ggg cta ttg gtc ttc ctc ctg att ata gca e Val Trp Asp Gly Leu Leu Val Phe Leu Leu Ile Ile Ala 75 80 85	893
	g tgg ctg cct tct tct gtg att ctg tca ctg tga aggaggg t Trp Leu Pro Ser Ser Val Ile Leu Ser Leu * 90 95	942

gcc	agaa	ata	aggt	gatc	ac a	gttg	gctg	a ga	tggt	tctc	aag	aaac	atg	ggtt	ttaaaa	1002
tgt	gtac	agt	gata	tctg	gt g	ccaa	acat	t gg	ctct	tcaa	att	gcta	ctt	aaaa	aaaaaa	1062
aa																1064
	<2	10>	52													
		11> 12>	710 DNA													
			Homo	sap	iens											
		20> 21>	CDS													
			(158) (682)											
atti		00>		acca	an a	atto	raca	ന നമ	acaai	caca	add	aacaa	rna (aaaa	ttgttg	60
															tctgct	120
					_				_						J	
caco	ctcc	gga	taaa	ccac	gg g	gtet	cccg	c gc	cgct	Me				o Va	c cgt l Arg 5	175
			ccc Pro 10													223
			ttg Leu													271
			cca Pro									_	_			319
			ggg Gly													367
			ttt Phe													415
			aag Lys 90													463
			atg Met													511

att aaa tat tot tgt oot aaa gga tac cga oto att ggt too tog tot 559

120 125 130	
gcc aca tgc atc atc tca ggc aac act gtc att tgg gat aat aaa aca Ala Thr Cys Ile Ile Ser Gly Asn Thr Val Ile Trp Asp Asn Lys Thr 135 140 145 150	607
cct gtt tgt gac agt gag ttg aaa tat gca ttc cta ttt ctt tta ccg Pro Val Cys Asp Ser Glu Leu Lys Tyr Ala Phe Leu Phe Leu Pro 155 160 165	655
ata cat tct aat ttt tct ctg gaa taa taaaa atctattccg aaaaaaaaaa	707
aaa	710
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taggggagcg cgctgctgtt tagagccacg agttaccgga gcgcctgatt cctgcgccga agtcagtggt ggccgaaagt ccggagtcgc tgtaaaacct gagattgtga gcc atg Met	120
taggggagcg cgctgctgtt tagagccacg agttaccgga gcgcctgatt cctgcgccga agtcagtggt ggccgaaagt ccggagtcgc tgtaaaacct gagattgtga gcc atg Met 1 gtg ggg aga tcc cgg cgc gga gca gct aag tgg gca gct gtg cga Val Gly Arg Ser Arg Arg Arg Gly Ala Ala Lys Trp Ala Ala Val Arg	120 176
taggggagcg cgctgctgtt tagagccacg agttaccgga gcgcctgatt cctgcgccga agtcagtggt ggccgaaagt ccggagtcgc tgtaaaacct gagattgtga gcc atg Met 1 gtg ggg aga tcc cgg cgg cgc gga gca gct aag tgg gca gct gtg cga Val Gly Arg Ser Arg Arg Arg Gly Ala Ala Lys Trp Ala Ala Val Arg 5 10 15 gcc aag gca ggt ccc acg ctc acc gac gaa aat gga gat gat tta gga Ala Lys Ala Gly Pro Thr Leu Thr Asp Glu Asn Gly Asp Asp Leu Gly	120 176 224
taggggagcg cgctgctgtt tagagccacg agttaccgga gcgcctgatt cctgcgccga agtcagtggt ggccgaaagt ccggagtcgc tgtaaaacct gagattgtga gcc atg Met 1 gtg ggg aga tcc cgg cgc gga gca gct aag tgg gca gct gtg cga Val Gly Arg Ser Arg Arg Arg Gly Ala Ala Lys Trp Ala Ala Val Arg 5 10 15 gcc aag gca ggt ccc acg ctc acc gac gaa aat gga gat gat tta gga Ala Lys Ala Gly Pro Thr Leu Thr Asp Glu Asn Gly Asp Asp Leu Gly 20 25 30 ttg cca ccc tca cca ggg gac acc agc tac tac caa gat cag gta gat Leu Pro Pro Ser Pro Gly Asp Thr Ser Tyr Tyr Gln Asp Gln Val Asp	120 176 224 272

-		_		-	atg Met	-	_		-	-		-				464
					gag Glu											512
			_	_	gct Ala		_			_		_	_	_		560
					ctt Leu 135											608
					caa Gln											656
					atc Ile											704
					gtc Val	-		-		_		-				752
					gct Ala											800
					aag Lys 215											848
	_		_		gaa Glu	-	-		_	_	_			_	-	896
		_			ttg Leu			_		_						944
				_	caa Gln		_			_					-	992
		_	_		atc Ile	_			-		-		_		_	1040
-		-			cat His 295		-		-			_			-	1088

•			cag aag ctg tcc Gln Lys Leu Ser	•
	Leu Thr Leu		gct gta aag aaa Ala Val Lys Lys 335	
-		-	cca aag tct gtt Pro Lys Ser Val 350	
			ctt tct gat gat Leu Ser Asp Asp 365	_
	_	Lys Tyr Tyr	aaa gaa ata gaa Lys Glu Ile Glu 380	
-			agc act gaa gaa Ser Thr Glu Glu	
	Asn Ala Lys		acc tat caa att Thr Tyr Gln Ile 415	•
			att gat cgc aat Ile Asp Arg Asn 430	_
			aaa att aga aga Lys Ile Arg Arg 445	
		Glu Glu Gln	cgt tat agt ggt Arg Tyr Ser Gly 460	-
			att aag ctt aaa Ile Lys Leu Lys	tga agt 1616 * 480
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aaaaaaaa				1685

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<213> Homo sapiens

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gag acg cat ctt cat aaa cag gca tac agg aca aac agt gaa gct gtt

Glu Thr His Leu His Lys Gln Ala Tyr Arg Thr Asn Ser Glu Ala Val
165 170 175

ggt tga aatcataatt aatgcgttac tgtatgaacc acaaaacagc actatttatt

881

Gly 180

941 tagcettact tetactteca gatgeagtge etettttgga gaagacatgt ttatttttea tgttctttct gacattactt tagcaattca acttgatgtg agaagaaaaa acaaatgttt 1001 caacacaaaa tctctgtttt gtgagaatac tgcactatgg aataattgac aaattgaaat 1061 ctcatatttg tcccaaaagt tgttttgagt tagttctacc tggtgcccat gttctgattg 1121 tgtgtgggat tgcatggtgt cctgattgca tctaggtgga gcggatggaa tgtgctgggc 1181 cactgttggg tggagagcag cacattctta cagaggagat ggagcgttat gagcatagta 1241 tgtggatagg tatcttcacc tgcccgcccc tgagtcagcc tccttgactt gatagcttga 1301 agaatccttt tccactgaaa tagaggataa ttaattgaca catctgaaat ccccaatcaa 1361 tcaatcaaga gaaaggtaga actaaaaact ccttaactta ctgttgctta cacccctgaa 1421 agtctgtttt taagcaaatg ggtaatagta gaaaataggt tagaatctat ggcttgatta 1481 aaaatatgtt attacattat catgttcagg attaggatta gtagtcagtt gctgtaaact 1541 attttgaaca aacagaaaag aacacggaaa catttttaac agagcattta attatgttgg 1601 aatacaggat cctagctctg tctgggaaca ttagtttatg tgagccagct ctatcagggt 1661 cttcccatgg tggttcagaa tagatgagca tagcatggtt ttgtttgttt ttgctttcaa 1721 ttttctaatt tggcatggat ccatatgtat ttactatcct ttttctaata tattaatata 1781 tgctacattt gtatttgcat tactataata ctttgagttg aaaaagagtt tcattgtgga 1841 gagaaaaagc aaatggtatg ccacaagatc actctgattt gagaaaaggg aggagggaa 1901 gatagtctga atggaaatct gaaatacgga atgttttaga gaaatatgtc acttgcatat 1961 2021 agaatgtttt aattgaggta taaattaatg agacaaagtg aaaaagaaat tatattcaga taggactgca ctacattatt tgtcacacat ggatctgtta ccatcaggtc aattcctagt 2081 atgcataaat tttttaaccc ttttaaaaga gacctatgtt gaaaacccct gaaaattcac 2141 tgaagaaaaa tcattactct ttttctcagt aaatcatatc atctgaaata ttacaaattt 2201 caaatttcta ggtgctatat taattcaata ttacaataac tcttacctaa ttattcttac 2261 aagttttaag ttgtggtagt ttagtgattt ttttaaaaaga tgtgtgaaat gttctctgca 2321 aaataattca ggccactgtc tccttttata tattattata attatttatt atgaagacca 2381

gtgaattacg atatttaaag tgagagaact taattatttg caaaggtaag ttacagcttg 2441
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15 20 25

gcc ctg aaa tgg cac ccg gat aaa aat ctg gat aat gcc gca gaa gca
Ala Leu Lys Trp His Pro Asp Lys Asn Leu Asp Asn Ala Ala Glu Ala
30 35 40

gct gaa caa ttt aaa tta atc caa gca gca tat gat gtg ttg agt gac 196 Ala Glu Gln Phe Lys Leu Ile Gln Ala Ala Tyr Asp Val Leu Ser Asp 45 50 55

cct cag gaa aga gca tgg tat gat aat cat aga gag gcc cta ctt aaa 244
Pro Gln Glu Arg Ala Trp Tyr Asp Asn His Arg Glu Ala Leu Leu Lys
60 65 70

ggt ggg ttt gat ggc gaa tat caa gat gac agc tta gat ttg cta cgc
Gly Gly Phe Asp Gly Glu Tyr Gln Asp Asp Ser Leu Asp Leu Leu Arg
75 80 85 90

tat ttc acc gtt acc tgt tat tct ggt tat gga gat gat gaa aag gga

Tyr Phe Thr Val Thr Cys Tyr Ser Gly Tyr Gly Asp Asp Glu Lys Gly
95 100 105

ttt tac acg gtg tat cgt aat gtt ttt gaa atg att gcc aag gaa gaa
Phe Tyr Thr Val Tyr Arg Asn Val Phe Glu Met Ile Ala Lys Glu Glu
110 115 120

cta gaa tct gtg tta gag gaa gag gtt gat gat ttc cca act ttt gga
Leu Glu Ser Val Leu Glu Glu Glu Val Asp Asp Phe Pro Thr Phe Gly
125 130 135

						gat Asp 145										484
						caa Gln										532
_		-	-	-		aac Asn	-		-		_	_	_	_		580
-			_			gac Asp		_								628
-	-	_	_	-	-	ttc Phe		_		_	_		_		_	676
		_				gaa Glu 225	_	_		_	_	-				724
_	_		_			cag Gln	_	_		_	_	-		_	_	772
	_		_	_	_	agc Ser		_		_	-					820
						gca Ala										868
_	-	-		_	_	gaa Glu	-		-			-			-	916
		_	_	_		gcc Ala 305		_	_				_	-		964
	_		_	_	_	aaa Lys	_		_		-	_	_	_	-	1012
			_		_	aag Lys			-	_		-	_			1060
	_				_	gaa Glu	_				_				-	1108
gaa	aat	cca	tta	gat	gac	aat	tct	gag	gaa	gaa	atg	gaa	gat	gca	cca	1156

Glu Asn Pro Leu Asp Asp Asn Ser Glu Glu Glu Met Glu Asp Ala Pro 365 370 375	
aaa caa aag ctt tct aaa aaa cag aag aca caa gaa aca gta aac cag Lys Gln Lys Leu Ser Lys Lys Gln Lys Thr Gln Glu Thr Val Asn Gln 380 385 390	1204
cac agg atg tac ctg gca aag att cat atc tgc ctg cag ctc act ttc His Arg Met Tyr Leu Ala Lys Ile His Ile Cys Leu Gln Leu Thr Phe 395 400 405 410	1252
aga tgg ctt ggg gaa aaa agt gtg tgt agg gag aga gaa ga	1300
aga gcg agc aca aat gtg cca aaa tgt tgc ttg aaa aca gac aga att Arg Ala Ser Thr Asn Val Pro Lys Cys Cys Leu Lys Thr Asp Arg Ile 430 435 440	1348
atg atg acc att tca atg taa at ggacctggac gaaggagtaa aggttgatcc Met Met Thr Ile Ser Met * 445	1401
atgaagatac taacttatat caagacagtg ccaaagaatt ggaagatagt ccccaggaaa	1461
atgtcagtgt cacagatgat cattacacca tgtgatgatc caaaaagtga agctaaaagg	1521
taagtcaaag ttgcatatta tttgtaaatt actgaatatt gatagtaagg atgtagcttt	1581
tcatatatca aataaaatct tctttcccat gactgaccag gtaatttaga tgtatctgta	1641
catatttatg tatagataca cacacata tgtatacaga tgaagagcgt tgagaagagg	1701
atgctagagg aatgtgccca cacacatctc agcagcatgg ccaaaatcag aaagatgtca	1761
ctttgatcca gttctcgttt accttatcct gctgtggcgc tgatctcgtc gtggatcatt	1821
aacacttgac actcacatga gaacaagact cctgctgcgt ccctggagtg tcactaagca	1881
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	 -	cat aga gag gcc His Arg Glu Ala 70	
	 _	gac agc tta gat Asp Ser Leu Asp 85	
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Met Lys Cys His Tyr Glu Ala Leu Gly Val

-		-		-		-		gag Glu	_		62	28
								gat Asp			67	76
	_			_	_	_	_	gag Glu	_	 	72	24

180

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Asp Thr Arg Gln Ala Ser Asn Arg Trp Glu Lys Arg Ala Met Glu Lys

580

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cca caa aca atg agt gtt ctt atc agc tgt aca acc tgc cat agt gaa Pro Gln Thr Met Ser Val Leu Ile Ser Cys Thr Thr Cys His Ser Glu 475 480 485 490	1492
ttt cca tct cgg aat aaa ctt ttt gac cat cta aag gcc aca ggt cat Phe Pro Ser Arg Asn Lys Leu Phe Asp His Leu Lys Ala Thr Gly His 495 500 505	1540
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cgt ttc ctg aac ccc gat gag gtg c Arg Phe Leu Asn Pro Asp Glu Val H 60 65											
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tcg gac ctg gag cca ccg ctg ttg gas Ser Asp Leu Glu Pro Pro Leu Leu G											
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		_		_				tac Tyr	_				-	-		821
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		_	_			_		ctg Leu 290		~	_		_			917
_				_				cag Gln	-	-		_		-		965
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	_			_	_	_	_	gcc Ala		-	-	-				1205
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Arg Asp Ile	_	s Leu Gly 1 5	Arg Lys Val 20	Pro Glu Ser	Leu Val 25	
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ETO CAR GIA	45	л стл ст <u>л</u> (Gly Gly Gly 50	GIA GIA GIA	GIA GIA	
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			Cys Ser Phe			

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			aac Asn													1047
			aat Asn 125													1095
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tcc cgc att gag act tat ggg ggc cgg cat cga gcc tct gct cag agc Ser Arg Ile Glu Thr Tyr Gly Gly Arg His Arg Ala Ser Ala Gln Ser 20 25 30	
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cgc cga cgc ctc cag cag tat gtc ccc ttt gcc agg ggt tct ggc cag Arg Arg Arg Leu Gln Gln Tyr Val Pro Phe Ala Arg Gly Ser Gly Gln 50 55 60 65	310
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aag gaa ctc acc aag gcc cat gag ctg gag gtg agg ctg cac act ttc Lys Glu Leu Thr Lys Ala His Glu Leu Glu Val Arg Leu His Thr Phe 100 105 110	454
agc atg ttt ggg atg ccc cgg ctg ccc cct gag gac cgg cgg cac tgg Ser Met Phe Gly Met Pro Arg Leu Pro Pro Glu Asp Arg Arg His Trp 115	502
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agg gag ctg gtg cct ggg cac aag gag atg agc cag gag ctc tgc cac Arg Glu Leu Val Pro Gly His Lys Glu Met Ser Gln Glu Leu Cys His 150 155 160	598

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					ctg Leu										ttt Phe	742
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					aag Lys 295											1030
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	Val		cga Arg													1510
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gcc tcc gag cga ggg aat gtg gtg gtg gaa aca ctc cac agg gcc cgg Ala Ser Glu Arg Gly Asn Val Val Val Glu Thr Leu His Arg Ala Arg 675 680 685	2182
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										gat Asp						319
										tca Ser 60						367
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			gac Asp													799
			acc Thr													847
			aaa Lys													895
			ttg Leu 245													943
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			tct Ser													1039
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tca Ser	aca Thr	gca Ala	aaa Lys	ttg Leu 310	agt Ser	tca Ser	aca Thr	aca Thr	caa Gln 315	aac Asn	aat Asn	act Thr	ggg Gly	aaa Lys 320	cct Pro	1135
gct Ala	act Thr	tcg Ser	tca Ser 325	gct Ala	aac Asn	cag Gln	aaa Lys	cct Pro 330	gtg Val	ggt Gly	ttg Leu	act Thr	ggt Gly 335	ctg Leu	gca Ala	1183
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			act Thr		Pro											1279

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			agt Ser													1375
			gga Gly 405													1423
			act Thr													1471
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cca Pro	gat Asp	gca Ala 25	gcc Ala	acc Thr	acc Thr	agc Ser	aga Arg 30	agc Ser	gat Asp	cag Gln	ctg Leu	acc Thr 35	cca Pro	caa Gln	Gl ^A aaa	271

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		gga Gly			_		-	-		415
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cga Arg gtg Val 35 gaa Glu	Thr ggc Gly 20 cgg Arg ctg Leu	Gly 5 tcg Ser cct Pro gag Glu gcc	ggc Gly ggc Gly ccc Pro	cct Pro ttc Phe gag Glu 55	tcc Ser ctg Leu 40	Leu gtg Val 25 agc Ser cgc Arg	Arg 10 ctg Leu acg Thr cgc Arg	Thr agc Ser gca Ala cgc Arg	Cgc Arg gag Glu Cgc Arg 60	Pro ctg Leu gag Glu 45 tac Tyr	Cag Gln 30 gag Glu gaa Glu	Pro 15 gac Asp acg Thr tac Tyr	gcg Ala ctg Leu gat Asp	tgg Trp gcc Ala agc Ser cac His 65	gtg Val gtg Val cga Arg 50 tgg Trp	152 200
gtg yal 35 gaa Glu gac Asp	Thr ggc Gly 20 cgg Arg ctg Leu gcg Ala	Gly 5 tcg Ser cct Pro gag Glu gcc Ala	ggc Gly ggc Gly ccc Pro atc Ile 70 cgg	Leu cct Pro ttc Phe gag Glu 55 cac His	tcc Ser ctg Leu 40 ctg Leu	Leu gtg Val 25 agc Ser cgc Arg ttc Phe	Arg 10 ctg Leu acg Thr cgc Arg cga Arg	Thr agc Ser gca Ala cgc Arg gag Glu 75 cgc	Leu cgc Arg gag Glu cgc Arg 60 aca Thr	Pro ctg Leu gag Glu 45 tac Tyr gag Glu cag	Cag Gln 30 gag Glu gaa Glu aag Lys	Pro 15 gac Asp acg Thr tac Tyr	gcg Ala ctg Leu gat Asp cgc Arg 80 gcc	tgg Trp gcc Ala agc Ser cac His 65 tgg Trp	gtg Val gtg Val cga Arg 50 tgg Trp	152 200 248

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			gat Asp		-						-	_				632
			atc Ile				_	-						_		680
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caga	cacc	ag a	atttg	gtgaa	ıt aa	agtt	gggg	g aat	ggad	cagc	ctaa	actgo	gga d	catto	gcagtg	790
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tcca	ıggtç	ıtg g	gctgc	gctgg	ja ca	cato	gtca	a aag	gtcac	aag	gccg	ggaç	gag t	ggtg	tcctt	910
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agg	gagc	cgg	tccg	ccgc	cg g	aacg	ggag	c ct	gggt	gtgc	gtg	tgga	gtc	cgga	ctcgtg	180
gga	gacg	atc (gcg	Me				l Le						r Le	g ttc u Phe	229
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											cgg Arg 40					325
											gga Gly					373
											gct Ala					421
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											gtc Val					517
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											ctc Leu					613
										-	cca Pro		_			661
											gtc Val					709
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		_	_	_		att Ile		_	_		_		-			1308
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_			_	_		cta Leu		_				_	_		00	1500
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						gaa Glu										1788
gct Ala						tca Ser										1836
agg Arg						caa Gln										1884

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2556

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485

500

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					act Thr											3036
_					agg Arg	_			-	_						3084
	_		_		caa Gln											3132
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_				-	att Ile			-						-	_	3228

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		aaa Lys 755														3324
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	~	gca Ala	_				_						_	_		3516
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		cat His		_			-	-				_		-	_	3660
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		gaa Glu 915														3804
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			aaa ggc caa tca Lys Gly Gln Ser 105	
			act gat gat tgc Thr Asp Asp Cys 120	
			gta atg cta aaa Val Met Leu Lys 135	
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	_		_	-	gtt Val 370	_					_	_				2474
-		-	_		gtg Val	-							_			2522
_	_		_		aag Lys				-		_		_	_	-	2570
_		_	-		tgt Cys				_	_	_	_	_			2618
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ctg	act	acc	tta	att	ggc	gct	gga	atc	cga	att	ctt	ttc	agt	tcc	tgc	2714

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aat gga gac ac Asn Gly Asp Th 40						-
atc gtt tcc tt Ile Val Ser Ph 55			_	_		
cag aaa gag ag Gln Lys Glu Ar	-	_		-		
ttc att gat ta Phe Ile Asp Ty 9				Pro Val I		
ggg tat ttc ct Gly Tyr Phe Le 105						
cga atg cta ct Arg Met Leu Le 120	eu Asp Ala (
ggc tgt acc gc Gly Cys Thr Al 135			-		-	
atc cct ctg ct Ile Pro Leu Le			_		-	
cat ggt gag ag His Gly Glu Se 17	er Ser Leu A			Leu Lys I		
att gaa tta at Ile Glu Leu Me 185				ttgtgacc	acaccga	tgg 933
agatacagaa aaa	agttaacg act	tggattct ato	cttcattt	tagactttt	tg gtctg	rtgggc 993
catttaacct gga	atgccacc at	tttatggg gai	taatgatg	cttaccato	gg ttaat	gtttt 1053
ggaagagctt ttt	tatttata gca	attgttta cto	cagtcaag	ttcaccato	gg ccgta	atcct 1113
tctaagggaa aca	actaaagt tg	ttgtagtc tc	catttcag	tcagaaact	ig atgtt	tcagc 1173
taggcacagt ggt	tacatgcc tg	t				1196

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gcaaattact taatctcagt aggcctcagt tctctctttc accaaatcag gagaattatt	180
tttttaatca tcaactgtac attattat atg caa aac ata ctg gta ggc att Met Gln Asn Ile Leu Val Gly Ile 1 5	232
atg tgg acc aaa aaa tat gac agc agg tgg tcc ttc cct ttt aag aaa Met Trp Thr Lys Lys Tyr Asp Ser Arg Trp Ser Phe Pro Phe Lys Lys 10 15 20	280
cta aga tat aca cac atg aag act gct ggt ggt gca agg tgt gga gtc Leu Arg Tyr Thr His Met Lys Thr Ala Gly Gly Ala Arg Cys Gly Val 25 30 35 40	328
att ggt gcc gtg ata gca gtg tgc agg tca gag cta gag agt cca gag Ile Gly Ala Val Ile Ala Val Cys Arg Ser Glu Leu Glu Ser Pro Glu 45 50 55	376
aag gga ctt tgc tgt ggg ctg aag tga ccagg aagggctccg tggaggaagt Lys Gly Leu Cys Cys Gly Leu Lys * 60 65	428
ggggcccaag gatggacagg acatggatgt ggcaggaaga gggagagcct taccagatgg	488
gccagacttc cggaaccaag atgttgctgg tgggatgtgt g	529
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gat ggg ggc gac ggc cag gcc ggg ccc gac gag ggc gag gtg gac tcc Asp Gly Gly Asp Gly Gln Ala Gly Pro Asp Glu Gly Glu Val Asp Ser 30 35 40	147											
tgc ctg cgg caa gga aac atg aca gct gcc cta cag gca gct ctg aag Cys Leu Arg Gln Gly Asn Met Thr Ala Ala Leu Gln Ala Ala Leu Lys 45 50 55 60	195											
aac ccc cct atc aac acc aag agt cag gca gtg aag gtg agt cgc aga Asn Pro Pro Ile Asn Thr Lys Ser Gln Ala Val Lys Val Ser Arg Arg 65 70 75	243											
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agg aag cat gtg gtg aag gag gtg cta ggg gag cac ata gtg ccc tcc Arg Lys His Val Val Lys Glu Val Leu Gly Glu His Ile Val Pro Ser 10 15 20	160											
gac cag cag att gtc agg gta ctc agg acc cca ggg aac aat ctg Asp Gln Gln Ile Val Arg Val Leu Arg Thr Pro Gly Asn Asn Leu 25 30 35	208											
cat gag gtg gag aca gcc caa ggg cag cgc ttc ctg gtg agc atg ccc His Glu Val Glu Thr Ala Gln Gly Gln Arg Phe Leu Val Ser Met Pro 40 45 50	256											
tcc aaa tac cgc aag aac atc tgg atc aag aga ggg gac ttt ctc att	304											

Ser Lys Tyr Arg Lys Asn Ile Trp Ile Lys Arg Gly Asp Phe Leu Ile 55 60 65 70												
gtt gac ccc att gaa gag gga gaa aag gtg aag gct gaa atc tcg ttt Val Asp Pro Ile Glu Glu Gly Glu Lys Val Lys Ala Glu Ile Ser Phe 75 80 85	352											
gtg ctc tgc aag gac cac gtg cgc tct ctg cag aag gag ggg ttt tgg Val Leu Cys Lys Asp His Val Arg Ser Leu Gln Lys Glu Gly Phe Trp 90 95 100	400											
cct gag gcc ttc tct gaa gtg gct gag aaa cac aac aac agg aac aga Pro Glu Ala Phe Ser Glu Val Ala Glu Lys His Asn Asn Arg Asn Arg 105 110 115	448											
caa act caa cca gaa ctc cca gct gag cca cag tta tca gga gag gag Gln Thr Gln Pro Glu Leu Pro Ala Glu Pro Gln Leu Ser Gly Glu Glu 120 125 130	496											
tcc agc tca gaa gat gat tct gac ctg ttt gtt aac aca aac cgc aga Ser Ser Ser Glu Asp Asp Ser Asp Leu Phe Val Asn Thr Asn Arg Arg 135 140 145 150	544											
cag tat cat gag agt gag gag gag agt gaa gag gag g	592											
gactccagga cccaattctc cacttgctca gggactggcc cctggctctt ctgggcttgg	652											
acatteccag ggtgetetge acatetteae eeetgeatga ggacaaagea gggeteetet	712											
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	107											
Met Ala Glu Ser Leu Arg Ser Pro Arg Arg Ser Leu Tyr Lys 1 5 10	107											
	107 155											

Glu Arg Met Arg	Asn Ser Arg 35	Asp Arg Leu Leu 40		g Gln 5
	Gly Pro Gly	aat tct cag aac Asn Ser Gln Asn 55		
		aat gct ttg cag Asn Ala Leu Gln 70		
		gag gag ctg ata Glu Glu Leu Ile		
		atc aac caa gag Ile Asn Gln Glu 105	Gln Ser Ile Il	
		ttt gat gaa aag Phe Asp Glu Lys 120		e Met
	Glu Ala Asn	cca ctc atc tgt Pro Leu Ile Cys 135		
		ggt gtg gtg gtg Gly Val Val Val 150		
		gag ttg aca gag Glu Leu Thr Glu		
		gag cac agt gca Glu His Ser Ala 185		
		gga aca gaa gaa Gly Thr Glu Glu 200		u Leu
	Ala Cys Asp	act tgg gct gtg Thr Trp Ala Val 215		ccagc 732
tgggactcac atca	ttctat gggcg	ttgaa gacaactcat	tcctctgagg ago	cttgtac 792
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160 165 155 761 gaa gaa aac agg ggt tac atg gaa att gaa cag tca gtg aaa tct ttt Glu Glu Asn Arg Gly Tyr Met Glu Ile Glu Gln Ser Val Lys Ser Phe 180 175 809 aag atg cca tcc tca aat ata gaa gag gaa gac agc cat ttc ttt ttt Lys Met Pro Ser Ser Asn Ile Glu Glu Glu Asp Ser His Phe Phe 190 195 857 cat ctt att att ttt gct ttt tgc att gct gtt gtt tac att aca tat His Leu Ile Ile Phe Ala Phe Cys Ile Ala Val Val Tyr Ile Thr Tyr 205 210 905 cac aac aaa agg aag att ttt ctt ctg gtt caa agc agg aaa tgg cgt His Asn Lys Arg Lys Ile Phe Leu Leu Val Gln Ser Arg Lys Trp Arg 225 230 220 953 gat ggc ctt tgt tcc aaa aca gtg gaa tac cat cgc cta gat cag aat Asp Gly Leu Cys Ser Lys Thr Val Glu Tyr His Arg Leu Asp Gln Asn 240 245 235 gtt aat gag gca atg cct tct ttg aag att acc aat gat tat att ttt 1001 Val Asn Glu Ala Met Pro Ser Leu Lys Ile Thr Asn Asp Tyr Ile Phe 255 260 250 1004 taa <210> 72 <211> 1562 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1244)..(1399) <400> 72 cttgagcagg ggttcactta ttctgagagc attagttctc ctaaaaagct ccagcataga 60 120 aagggaagat aaaccaaatt ctagcttgtg ttttacccac agaaggatac aggacaaagg aatagtaact ggcctgtttg gatactaaaa ttgaaaataa cttttagcct cctccttatg 180 240 atagccgcca gagtaaatgt tgagcattac tacagaaaag ccacaaacca agaatctacc tgtttggaaa gatcttttgc atctctgaag gtgcttaaag catacttagt gcctttcctt 300 360 ttaactqqqa aqataaaaqa agtatctgtc caagatatta atatgtaaga taacattgta 420

qacatqttct tctgataata caaggtttat tctatttgca ttaggatatt tgtggacatg

480 tccatctaat ataaaqqaaa gttttttaat cattgaggca tgtagggctg agttatataa 540 tgtagaaact tctaaagata attggatgag aatatacata ttgacctgta tattatgact 600 aatcatgact cagatcttaa tacagggatg atctcatagc atttagatat cagaaaaggt tttgacctat atgtctttaa tattgtttga atacatgtat aatctttatc attcctcagt 660 720 gtttcatttc tcaaattctg taaaaggaat ataagaggaa agacaattca tatacaaaga 780 caacgagatt aaaaatatgc agtaggaaaa ataattactt aaggggagat tttttttaca 840 tgaaatctgg gctttggatg tgtgtgtgtg tgtgtgtgtg cacatatgca ctgtggtggg agtggggcaa cttggggaat atgttacatg tgtgactttg ttttgccctg gcgaagttaa 900 960 tgttgttcag aaagggtaaa tgtttggaca cttgcaattg ctcatggatg aatttatatg 1020 ttttagtcat agaaaaattg taccetttga tagaagcaca ttttctttcc aaagttggtt attaaccaca gaattatagc aggtattcat aacttaagtt tgaaaatcaa tagcgtctgc 1080 aaatggatta acagattaga gaatcaacag catcggaaaa taggttaatg catattgctt 1140 1200 ctaacaagtg catgaagaaa tagaagaagc tatgtagctt tcagttctga cagaaaaggg 1255 tgaaggaggg tatcatttca agaaaaaaaa tagctatcac gca atg gtt atc tct Met Val Ile Ser 1 1303 gaa aat att tgt att aag atg tgt ata cat ggc cag gca tgg tgg ctc Glu Asn Ile Cys Ile Lys Met Cys Ile His Gly Gln Ala Trp Trp Leu 10 20 5 1351 atg cct gta atc cca gca ctt tgg gag gca ggt gga tca cga ggt cag Met Pro Val Ile Pro Ala Leu Trp Glu Ala Gly Gly Ser Arg Gly Gln 25 1399 gag atc aag acc atc ctg gcc aac atg gtg aaa cct cat ctc tac taa Glu Ile Lys Thr Ile Leu Ala Asn Met Val Lys Pro His Leu Tyr aaatacaaaa atgagcgggg tgtggtggcc catgcctgta gtcccagctg ctcgggagac 1459 1519 tgaatctctt gagcctggga agcagaggtt gcagtgaact gagatcgcgt cactgcactc

cagcccgggt gacagagcga gattccatct caaaaaaaaa aaa

1562

<210> 73

<211> 2100

<212> DNA

<213> Homo sapiens

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cca agt tac tta aaa atc acc tgt ggt aaa aga agc aag cag atc acc
Pro Ser Tyr Leu Lys Ile Thr Cys Gly Lys Arg Ser Lys Gln Ile Thr
10 15 20

ccc atc tac tat ccc tcc cgc ctc ccc cct gtc aaa aga aag ttc tca 1348 Pro Ile Tyr Tyr Pro Ser Arg Leu Pro Pro Val Lys Arg Lys Phe Ser 25 30 gtt tat gat gca aaa ctt aca att gtt cat tta tcc aca ttc tca ata 1396 Val Tyr Asp Ala Lys Leu Thr Ile Val His Leu Ser Thr Phe Ser Ile 45 50 55 1446 gag gat ttt cca cta tat tta agt atg gca gga taa ttac ccacctgttc Glu Asp Phe Pro Leu Tyr Leu Ser Met Ala Gly * 60 ctcttttcag cttagaaaca taacggttca ttccttttat tgctagagaa tgtcattcct 1506 gaagatttta taaacaaagg caaatatgaa ggaaaatttg taattatgaa ataagtcctt 1566 1626 tgtagtaaag aatatttccc aaatcataac agttctattt ggaatgatac ccacaactct acaagcatct tatccctcta caggaatgac taccttatta attaaaataa aaatttaaca 1686 aggatcaaaa taaaattctt tagcaataga ctcctgcaaa aataaaaact aaaactagac 1746 1806 ctagtcattg ccatttgatc aaacttagaa caggcttaaa taacagaacc actccattaa agaggcatag aaagaaaagt ttactaaaat aaatgtaaaa gtcttatgga gatgaagatc 1866 tctagaatag tcttaagtct atgactactg ctatcattaa tgagcaaata aatgacttga 1926 aattattccn cctggaaaag gtaaactcat acgtattatg gaaaangcct atgggcactt 1986 agaaaaatat tcctgggtaa gtaaaccatg gnaaatatag ggtacatcct aagcctctcc 2046 2100 gccctaactt ttaaaattat tnttggagaa aggatagcac tagccgggga ggaa

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<211> 933

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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<400> 74

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Met Pro Leu Ile Leu Ser Leu Gln Val 1 5

tgc Cys 10																341
ccg Pro																389
atg Met	~ ~	~		_			_	_			-	-				437
ttt Phe																485
ctc Leu																533
gag Glu 90																581
aat Asn																629
aag Lys																677
cgc Arg																725
ctg Leu														_	_	773
ggc Gly 170																821
gtc Val														tga * 200	ggc	869
tgga	cato	egg o	cccg	ctcc	cc a	caato	gaaat	c aaa	agtta	attt	tcto	catto	ccc a	aaaa	aaaaa	929
aaaa	L															933

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								gtc Val 130								856
								cgt Arg								904
								gac Asp								952
								ggc Gly								1000
								gag Glu								1048
								cag Gln 210								1096
_		_		-			_	cag Gln								1144
_				_				gca Ala					_	_		1192
_	_		_			-	_	gag Glu			_				_	1240
_		_			_		-	acc Thr		_	-					1288
-	_		_	~ ~	_	_		cag Gln 290		_			_		-	1336
	_		_	_				tgg Trp	-	-			-	_	_	1384
_	_				_	_		ggc Gly	_	-	-					1432
								act Thr								1480
gag	aat	gag	ctg	ggc	atc	aca	ccg	gtg	gtg	tct	gca	cag	gcc	gtg	gta	1528

Glu	Asn	Glu	Leu	Gly 350	Ile	Thr	Pro	Val	Va1 355	Ser	Ala	Gln	Ala	Val 360	Val	
					ctg Leu											1576
_	_		_	_	atg Met	-										1624
					agt Ser	_	_				~			_		1672
					cgg Arg 415											1720
_	_	_	_	_	gag Glu	_		-				-				1768
		-			cct Pro		-		_							1816
					Gly ggg											1864
	_	_	-	_	ctc Leu	-	-								_	1912
-		-	-		acc Thr 495	-		_		_						1960
					gat Asp											2008
_		-			gag Glu	-		_	_	_						2056
					agt Ser											2104
					gag Glu											2152
					atc Ile											2200

570	575	580		585
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cct ccc cgc agc to Pro Pro Arg Ser C 605				_
ttt gtg ggc tgg gg Phe Val Gly Trp G 620			0 0	9
atg gag aag gag ga Met Glu Lys Glu G 635		Pro Phe Ser S		
gaa gat gtg cct tt Glu Asp Val Pro Le 650				
gcc aag acc tca gg Ala Lys Thr Ser Gl 67	y Thr Met Asn			
ctg ctg cgc cgt gc Leu Leu Arg Arg Al 685				
cag acc atc caa co Gln Thr Ile Gln Ar 700				
cta gag gcc gag gg Leu Glu Ala Glu Gl 715		Glu Leu Ala I		
agt tcc cca gaa ca Ser Ser Pro Glu Gl 730				
ctc gtt gac aag aa Leu Val Asp Lys Ly 75	s Asn Ser Leu			
atc acg gtg cag ga Ile Thr Val Gln Gl 765				
cag gag cta cga gg Gln Glu Leu Arg Gl 780				
gct gat cgg cag gc Ala Asp Arg Gln Al 795		Val Leu Arg L		

gto Val 810	Asr	caq Glr	g aga 1 Arg	gat Asp	gcc Ala 815	Leu	ato Ile	cgc Arg	tto Phe	cag Gln 820	Glu	g gag ı Glu	g cgo L Arg	agg Arg	g ctc g Leu 825	2920
agc Ser	gag Glu	rctg Leu	g gcc 1 Ala	ttg Leu 830	Gly	aca Thr	Gly	gcc Ala	cag Gln 835	. Gly	tag	, acç	ra go	gtgg	igccg	2970
tct	gctt	tcg	ttcc	caca	aa g	aaag	cacc	t ca	cccc	agca	cag	rtgcc	acc	ccto	ıttcatc	3030
tgg	gctg	cct	ggca	gaga	gc c	ttgc	tgtt	t ac	aatt	aaaa	tgt	ttct	gcc	aaaa	ıaaaaaa	3090
aaa																3093
	.0	1.0-	7.6													
		10> 11>	76 1110													
		12> 13>	DNA Homo	ຕລກ	iane											
			TIOIIIO	sap.	rens											
	_	20> 21>	CDS													
			(179) (9	961)											
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atg Met	cca Pro	cag Gln	aat Asn	gaa Glu	tat	att	gaa Glu	tta	cac Hic	cgt	aaa	cgc	tat	gga	tac	226
1	110	GIII	nan	5	тУT	116	GIU	пеп	10	Arg	гуя	Arg	Tyr	15	Tyr	
cgt	ttg	gat	tac	cat	gag	aaa	aag	aga	aag	aaq	gaa	agt	cga	σaσ	act	274
Arg	Leu	Asp	Tyr	His	Glu	Lys	Lys	Arg	Lys	Lys	Glu	Ser	Arg	Glu	Ala	/-
			20					25					30			
cat His	gaa Glu	cgt Ara	tca Ser	aag Lvs	aag Lys	gca Ala	aag	aaa	atg Met	att	ggt Gly	ctg	aag	gct	aag	322
		35	501	27.0	_, 0	1114	40	цу	ricc	116	GIY	45	пур	AIA	пур	
ctt	tac	cat	aaa	cag	cgt	cat	gct	gag	aaa	ata	caa	atg	aaa	aag	act	370
Leu	Tyr 50	His	Lys	Gln	Arg	His 55	Ala	Glu	Lys	Ile	Gln	Met	Lys	Lys	Thr	
											60					
atc Tle	aag Lvs	atg Met	cat His	gaa Glu	aag Lws	aga Ara	aac Asn	acc Thr	aaa	caa Gln	aag	aat	gat	gaa	aag	418
65	-2 -				70	9			J D	75	шy	ASII	ഹാവ	GIU	80 80	
aca	cca	cag	gga	gca	gta	cct	gcc	tat	ctg	ctg	gac	aga	gag	gga	caa	466
Thr	Pro	Gln	Gly	Ala 85	Val	Pro	Ala	Tyr	Leu 90	Leu	Asp	Arg	Glu	Gly	Gln	
				55					J (95		

tct cga gct aaa gta ctt tcc aat atg att aaa cag aaa aga aaa gag Ser Arg Ala Lys Val Leu Ser Asn Met Ile Lys Gln Lys Arg Lys Glu 100 105 110	514
aag gcg gga aaa tgg gaa gtc cct ctg cct aaa gta cgt gcc cag gga Lys Ala Gly Lys Trp Glu Val Pro Leu Pro Lys Val Arg Ala Gln Gly 115 120 125	562
gaa aca gaa gta tta aaa gtt att cga aca gga aag aga aag aag aag Glu Thr Glu Val Leu Lys Val Ile Arg Thr Gly Lys Arg Lys Lys 130 135 140	610
gca tgg aag aga atg gtt act aaa gtg tgc ttt gtt gga gat ggc ttt Ala Trp Lys Arg Met Val Thr Lys Val Cys Phe Val Gly Asp Gly Phe 145 150 155 160	658
aca aga aaa cca cct aaa tat gaa aga ttc atc agg cca atg ggc ttg Thr Arg Lys Pro Pro Lys Tyr Glu Arg Phe Ile Arg Pro Met Gly Leu 165 170 175	706
cgt ttc aag aaa gcc cat gta aca cat cct gaa ctg aaa gcc acc ttt Arg Phe Lys Lys Ala His Val Thr His Pro Glu Leu Lys Ala Thr Phe 180 185 190	754
tgc cta cca ata ctt ggt gta aag aag aat ccc tca tcc cca ctg tat Cys Leu Pro Ile Leu Gly Val Lys Lys Asn Pro Ser Ser Pro Leu Tyr 195 200 205	802
aca act ttg ggt gtt att acc aaa ggt act gtc att gaa gta aat gtg Thr Thr Leu Gly Val Ile Thr Lys Gly Thr Val Ile Glu Val Asn Val 210 215 220	850
agc gaa ttg ggc ctt gtg aca caa gga ggc aaa gtt att tgg gga aaa Ser Glu Leu Gly Leu Val Thr Gln Gly Gly Lys Val Ile Trp Gly Lys 235 240	898
tat gcc cag gtt acc aac aat cct gaa aat gat gga tgt ata aat gca Tyr Ala Gln Val Thr Asn Asn Pro Glu Asn Asp Gly Cys Ile Asn Ala 245 250 255	946
gtc tta ctg gtt tga cagcaatttc atatataatt attgaggact acacaccaat Val Leu Leu Val * 260	1001
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<211> 1835

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<213> Homo sapiens

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gct agg aaa gtg gtc tta gcc tgg gga ctc cta aat gta tct atg gct Ala Arg Lys Val Val Leu Ala Trp Gly Leu Leu Asn Val Ser Met Ala 25 30 35 40	148
gga atg ata tat act gaa atg act gga aaa ttg att agt tca tac tac Gly Met Ile Tyr Thr Glu Met Thr Gly Lys Leu Ile Ser Ser Tyr Tyr 45 50 55	196
aat gtg aca tac tgg ccc ctc tgg tat att gag ctt gcc ctt gca tct Asn Val Thr Tyr Trp Pro Leu Trp Tyr Ile Glu Leu Ala Leu Ala Ser 60 65 70	244
ctc ttc agc ctt aat gcc tta ttt gat ttt tgg aga tat ttc aaa tat Leu Phe Ser Leu Asn Ala Leu Phe Asp Phe Trp Arg Tyr Phe Lys Tyr 75 80 85	292
act gtg gca cca aca agt ctg gtt gtt agt cct gga cag caa aca ctt Thr Val Ala Pro Thr Ser Leu Val Val Ser Pro Gly Gln Gln Thr Leu 90 95 100	340
tta ggg ttg aaa aca gct gtt gta cag act acg cct cca cat gat ctg Leu Gly Leu Lys Thr Ala Val Val Gln Thr Thr Pro Pro His Asp Leu 105 110 115 120	388
gca gca acc caa atc cct ccc gct cca cct tcc cct tca att cag ggt Ala Ala Thr Gln Ile Pro Pro Ala Pro Pro Ser Pro Ser Ile Gln Gly 125 130 135	436
cag agt gtg ttg agt tat agc cct tct cgt tcg ccc agt acc agt ccc Gln Ser Val Leu Ser Tyr Ser Pro Ser Arg Ser Pro Ser Thr Ser Pro 140 145 150	484
aag ttc acc acc agc tgt atg act ggt tac agc cct cag ctg caa ggt Lys Phe Thr Thr Ser Cys Met Thr Gly Tyr Ser Pro Gln Leu Gln Gly 155 160 165	532
ctg tcc tca ggt ggc agt ggt tct tat agc cct gga gtg acc tac tcg Leu Ser Ser Gly Gly Ser Gly Ser Tyr Ser Pro Gly Val Thr Tyr Ser 170 175 180	580
ccc gtc agt ggt tat aat aag ttg gcg agc ttt agc ccc tct cctPro Val Ser Gly Tyr Asn Lys Leu Ala Ser Phe Ser Pro Ser Pro Pro185190195200	628
tct ccg tac cct acc act gtt gga cca gtg gag agc agt gga ttg aga	676

Ser	Pro	Tyr	Pro	Thr 205	Thr	Val	Gly	Pro	Val 210	Glu	Ser	Ser	Gly	Leu 215	Arg	
	_		_		tca Ser			_						_		724
_	_		_		gac Asp		_		_	-						772
-				-	cat His		-	_	_		_		-			820
					cct Pro 270											868
-		-			tta Leu	-	-		-		_		-	_		916
	_	_		_	gct Ala			~	_	_	_		_			964
					gtc Val											1012
	-		_	-	tca Ser			_			_					1060
					cca Pro 350		-							-		1108
					ggt Gly											1156
					caa Gln											1204
	-				gtt Val	_			_					_	-	1252
					atc Ile											1300
					aga Arg											1348

425	430	435	440
aca gac ctg ccc acc Thr Asp Leu Pro Thr 445	Asp Ser Ala Ile Ile	e Met His Val Phe	-
tac ctt gat tcc aga Tyr Leu Asp Ser Arg 460	_		
act ttt act tct cag Thr Phe Thr Ser Gln 475			
aca aat gag aat gtt Thr Asn Glu Asn Val 490	_		
cat tat gag ctc atc His Tyr Glu Leu Ile 505	5 5 5	~	~ ~ ~
aga aat aat atg ttt Arg Asn Asn Met Phe 525		Phe Leu Tyr Ile	•
acc aaa gag tca gga Thr Lys Glu Ser Gly 540			
gtg aat ata ttg tgg Val Asn Ile Leu Trp 555		g c aagtcatata ttt	aattctg 1735
acatttagac tatttcact	tg aaccagaagt cgaaac	ctaaa catctctgag c	cactgactc 1795
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<211> 1029

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (428)..(817)

<400> 78

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aattgaagaa aaaaggccaa gttaaaatag gaaaacaaat ggttttcatt tggtggcagt 180

tgaaatcaaa gtatacatgt gtatacattc taatccgtca tctatcccat gtggcatttt 240 ccaaggtttt aagagtctac caggccaaac cctttqccac tttcactqct tttqctttqc 300 ttttcccctt tctttctct cgctttgcct tcagcctttt tctttgcctt tggttcatcc 360 atattgggta ctgtccatgc tggtcggcgt gagcgtgagg tgtgggtgtt cgtttctcag 420 gtaaaac atg gct aaa agc tta cgg agt aag tgg aaa aga aag atg cgt 469 Met Ala Lys Ser Leu Arg Ser Lys Trp Lys Arg Lys Met Arg gct gaa aag aga aaa aag aat gcc cca aag gag gcc agc agg ctt aaa 517 Ala Glu Lys Arg Lys Lys Asn Ala Pro Lys Glu Ala Ser Arg Leu Lys 15 2.0 25 agt att ctc aaa cta gac ggt gat gtt tta atg aaa gat gtt caa gag 565 Ser Ile Leu Lys Leu Asp Gly Asp Val Leu Met Lys Asp Val Gln Glu 35 ata gca act gtg gtg gta ccc aaa ccc aaa cat tgc caa gag aaa atg 613 Ile Ala Thr Val Val Val Pro Lys Pro Lys His Cys Gln Glu Lys Met 50 caa tgt gag gta aaa gat gaa aaa gat gac atg aaa atg gag act gat 661 Gln Cys Glu Val Lys Asp Glu Lys Asp Asp Met Lys Met Glu Thr Asp att aag aga aac aaa aag act ctt cta gac cag cat gga cag tac cca 709 Ile Lys Arg Asn Lys Lys Thr Leu Leu Asp Gln His Gly Gln Tyr Pro 85 ata tgg atg aac caa agg caa aga aaa agg ctg aag gca aag cga gag 757 Ile Trp Met Asn Gln Arg Gln Arg Lys Arg Leu Lys Ala Lys Arg Glu 100 105 aaa aga aag ggg aaa agc aaa gca aaa gca gtg aaa gtg gca aag ggt 805 Lys Arg Lys Gly Lys Ser Lys Ala Lys Ala Val Lys Val Ala Lys Gly 115 120 ttg gcc tgg tag act cttaaaacct tggaaaatgc cacatgggat agatgacgga 860 Leu Ala Trp 130 ttagaatgta tacacatgta tactttgatt tcaactgcca ccaaatgaaa accatttgtt 920 ttcctatttt aacttggcct tttttcttca attcaaaccc agcataactc ctcaagtttg 980 ttttgggaac ttgaataaaa tattttcttt gatacaaaaa aaaaaaaaa 1029

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<212> DNA

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atg aaa ggt act aaa gtg aag act cct gaa atg att att cag aaa cct

757

M	T	Q1	ml	T	77- T	T	ml	D	α1	Mot	т1 -	т1 ~	Λ1	T	Daca	
Met 175	ьуs	GΤĀ	Tnr	ьуs	Val 180	ьуѕ	Tnr	Pro	GIU	Met 185	TTE	тте	GIN	ьуѕ	190	
					gat Asp											805
					gtt Val											853
					ctt Leu											901
					ttg Leu							_				949
				_	agg Arg 260			_		_	_	_				997
-	_				aaa Lys			-	_	_				_	_	1045
-			-		gtc Val		_	_	_	_	_					1093
_	_	_	_		gat Asp	_	_					_			_	1141
	_		-	_	aaa Lys	_		-		_				-		1189
					gtt Val 340											1237
					gtc Val											1285
					ctt Leu											1333
					aag Lys											1381
					aag Lys											1429

		400					405					410					
G			_			ggc Gly 420				-		-	-		_		1477
_		-				gac Asp			_	_	_		_	_		_	1525
				_		cca Pro				_				_		_	1573
_	_		_		_	gct Ala	_		-					_		-	1621
_			-		-	gtg Val	_			_		_			_		1669
G						atg Met 500									-		1717
						gac Asp											1765
						atg Met		-	-	-	_				_		1813
						agt Ser											1861
						gac Asp											1909
Ρ						cct Pro 580											1957
						gct Ala											2005
						gtg Val											2053
						atg Met											2101

	-		-		gac Asp	_		_					-	-		214	.9
_		_	_		gtg Val 660		~	~	~		_	~				219	7
					gcc Ala											224	.5
	_	-	_		aag Lys			_				_	_		_	229	3
					cca Pro	-		-			_					234	.1
					cca Pro						-		_	_	_	238	9
	_			_	ggg Gly 740	_	-			_	-		_	_		243	7
					gct Ala											248	5
					aaa Lys	_				-	-			_		253	3
				-	atg Met	_	_		-		-		_			258	1
_	_	_			gca Ala		_		_				_	_		262	9
_	_				aag Lys 820	_		_		_		_	_		_	267	7
					cca Pro	-		_			~		_	-	_	272	5
_	_	_			ccc Pro	_		-		_	-		-		-	277	3

					ggg											:	2821
				_	acc Thr		_			_		-		-		2	2869
	-				aaa Lys 900	_			-		_					2	2917
					atg Met											2	2965
	-			_	gcc Ala		_			-				-		3	3013
	_	_	_		aag Lys	_		-		_		-	-			3	3061
					cga Arg											3	3109
					ccc Pro 980											3	3157
					gga Gly			Lys					Lys			3	3205
	_	His		_	gcc Ala		Lys			_		Asp		~	~	3	3253
	Leu	_			aaa Lys	Leu	_		-		Asp			_		3	3301
Glu	_	_		-	atg Met 1				-	Val	-					3	3349
	-	-		Ser	gct Ala 1060		_		Asp	_				Asp		3	3397
	_	_	Met		aag Lys			Met		-		_	Met			3	3445
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Phe Lys Gly	Glu Gly 1090	Pro Glu	Val Asp 1095	Val Lys		Lys Ala 100	Asp
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att gaa ggt Ile Glu Gly 1120	-	-		Gly Pro			
gaa atg agt Glu Met Ser 1135	Ile Lys	-	-		-	Val Gly	-
cat ttg aaa His Leu Lys		-	Lys Gly	-		_	
aaa gta gaa Lys Val Glu					Asp Ile		
aaa gtt gat Lys Val Asp 1185		Ala Pro .					
cac ctg aag His Leu Lys 1200	-		-	Pro Lys	_	•	
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ctt ggt gtt Leu Gly Val			Val Asp				
ctt gaa gct Leu Glu Ala					Lys Phe 1		
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aat ttg aaa Asn Leu Lys 1280		_		Asp Val			
aaa gtg gaa Lys Val Glu 1295	Gly Asp					Lys Ala	
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1315 1320 1325

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				gaa ggt gaa a Glu Gly Glu M	-
		Ile Lys Gly		gac att gat g Asp Ile Asp A	
				aaa atg ccc a Lys Met Pro I 1405	
			Gly Phe Lys	gca gag ggc c Ala Glu Gly F 1420	
	Val Asn Leu		Asp Ile Asp	gtg tct gga c Val Ser Gly F .435	
	Thr Asp Ala			gga cca gaa g Gly Pro Glu G	
		Phe Lys Met		aat ata aaa g Asn Ile Lys A 14	
	Ser Met Pro	Asp Val Asp		aag gga ccc a Lys Gly Pro I 1485	
Leu Lys Gly			Pro Glu Leu	gaa ggt gat c Glu Gly Asp I 1500	
	Gln Val Asp		Pro Leu Val	gaa gcg gag g Glu Ala Glu V 515	
	Asp Leu Glu	-		aag ggc ccc a Lys Gly Pro L	•
		_		atc tcc atg c Ile Ser Met P 15	

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ggg ccc aag ttt aag atg cct gag atg cac ttc Gly Pro Lys Phe Lys Met Pro Glu Met His Phe 1600 1605		5029
tcc atg cct gat gtg aac tta aac ttg aaa ggc Ser Met Pro Asp Val Asn Leu Asn Leu Lys Gly 1615 1620 1625		5077
gat atg gat gtg tct gtt ccc aaa att gga ggg Asp Met Asp Val Ser Val Pro Lys Ile Gly Gly 1635 1640		5125
cag tgt gga tgt gga ggt gcc tga tgttgagctg g Gln Cys Gly Cys Gly Gly Ala * 1650	gctgtcgttg ttctgagggc	5179
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				gtg Val									208
			 	ctg Leu		_						~ ~	256
				gtg Val 60									304
				tat Tyr									352
_		_		aac Asn	_		-				_		400
	-		 _	aac Asn	~	~		_			 		448
				tgg Trp									496
				cca Pro 140									544
				gaa Glu					-	-			592
				gat Asp									640
				tac Tyr									688
				ccg Pro									736
				atg Met 220									784

aaaaaaaaa aa

						att Ile						_				832
						att Ile		_		_			_	_		880
						gac Asp										928
_						gag Glu 285					_	_		-	_	976
						aaa Lys										1024
						tct Ser										1072
						cga Arg				_			_		_	1120
						tgg Trp										1168
						ggc Gly 365				-						1216
						ctc Leu										1264
						gcc Ala										1312
						agc Ser										1360
						ctt Leu										1408
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caco	cctca	aag	cttc	aggt	ga g	ctga	gctt	c ta	acac	tacc	atc	aaag	caa	ctgg	aacccc	180
ttga	aatt	tga	tttc	tgga	ga c	gcga	gcat	a at	cctt	ttgc	aaa	catc	tca .	acgc	tggctc	240
tcca	aggt	gga ·	gcac	Me				р Су						s Ty	t ctg r Leu	291
					ttc Phe											339
					gtc Val			-								387
					ctg Leu 50			-		_				_	_	435
					ttt Phe											483
					tgt Cys										ctg Leu	531
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					cga Arg											627
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														gac Asp 155		723
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														ttc Phe 235		963
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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (264)..(1508)

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aactatttgt agagaatcac tgatccggcc tgcaagcatt ttgcacggca aaaatatcga	180
tcagtgttaa gtgaagatca cattttatat gcgatcttga cttttttgtc ttacattata	240
tttttataga ttttgttata aac atg gtg ctg gga aag gtg aag agt ttg Met Val Leu Gly Lys Val Lys Ser Leu 1 5	290
aca ata agc ttt gac tgt ctt aat gac agc aat gtc cct gtg tat tct Thr Ile Ser Phe Asp Cys Leu Asn Asp Ser Asn Val Pro Val Tyr Ser 10 15 20 25	338
agt ggg gat acc gtc tca gga agg gta aat tta gaa gtt act ggg gaa Ser Gly Asp Thr Val Ser Gly Arg Val Asn Leu Glu Val Thr Gly Glu 30 35 40	386
atc aga gta aaa tct ctt aaa att cat gca aga gga cat gcg aaa gta Ile Arg Val Lys Ser Leu Lys Ile His Ala Arg Gly His Ala Lys Val 45 50 55	434
cgc tgg act gaa tct aga aac gcc ggc tcc aat act gcc tat aca cag Arg Trp Thr Glu Ser Arg Asn Ala Gly Ser Asn Thr Ala Tyr Thr Gln 60 65 70	482
aat tac act gaa gaa gta gag tat ttc aac cat aaa gac atc tta att Asn Tyr Thr Glu Glu Val Glu Tyr Phe Asn His Lys Asp Ile Leu Ile 75 80 85	530
ggg cac gaa aga gat gat gat aat tcc gaa gaa ggc ttc cac act att Gly His Glu Arg Asp Asp Asp Asn Ser Glu Gly Phe His Thr Ile 90 95 100 105	578
cat tca gga agg cat gaa tat gca ttc agc ttc gag ctt cca cag aca His Ser Gly Arg His Glu Tyr Ala Phe Ser Phe Glu Leu Pro Gln Thr 110 115 120	626
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gtg aaa gcc gaa ttg cac agg cct tgg cta cta cca gta aaa tta aag Val Lys Ala Glu Leu His Arg Pro Trp Leu Leu Pro Val Lys Leu Lys 140 145 150	722
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ctg tca ccc caa gca ggc aca aaa gaa aag aca ctc tgt tgc tgg ttc Leu Ser Pro Gln Ala Gly Thr Lys Glu Lys Thr Leu Cys Cys Trp Phe 170 175 180 185	818
tgt acc tca ggc cca ata tcc tta agt gcc aaa att gaa agg aag ggc Cys Thr Ser Gly Pro Ile Ser Leu Ser Ala Lys Ile Glu Arg Lys Gly	866

			190					195					200		
			 -	tca Ser		-			-					_	914
				gtg Val									_	_	962
				aaa Lys									-		1010
				tta Leu 255											1058
				cca Pro											1106
				tat Tyr											1154
				ctt Leu											1202
				agc Ser											1250
				ctc Leu 335						-	-		_	_	1298
		_	_	gaa Glu		-			_						1346
				gct Ala	-	-	_			_	-				1394
				atc Ile											1442
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Ile Phe *

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<210> 84

<211> 2885

<212> DNA

<213> Homo sapiens

<220>

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<400> 84

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					ctt Leu											836
_				-	tac Tyr 90		-			-				_		884
					atg Met	_	-						_		_	932
_	-		-		agg Arg			_		_				_	_	980
					acc Thr											1028
					cac His											1076
					ccc Pro 170			_			_		_			1124
					ctc Leu											1172
					tgt Cys											1220
_	_	_			cag Gln	_	_									1268
_	-		_		aag Lys	_		-	_	~	_	_		_		1316
					aca Thr 250											1364
ata Ile	taa *	aacg	gtttt	.gc t	aaga	igttt	a aa	iatct	taaa	acc	cata	ıagt	gcca	ıctaç	jga	1420
aggaaaccct gtatatacct acattgaccc aagaaatatt tacgcaatcc ctagcagaac 14												1480				
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gta ggt tat ggg gac agt aag gat tgt atc ctg gag ccg ctt tcc ctg Val Gly Tyr Gly Asp Ser Lys Asp Cys Ile Leu Glu Pro Leu Ser Leu 15 20 25 30	155												
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cct tgt att ttc tgt gaa gaa cat ttt cct gtg gct gaa caa gac aaa Pro Cys Ile Phe Cys Glu Glu His Phe Pro Val Ala Glu Gln Asp Lys 50 55 60	251												
ctt ctg aag cac atg att att gag cat aag att gtc ata gct gat gtc Leu Leu Lys His Met Ile Ile Glu His Lys Ile Val Ile Ala Asp Val 65 70 75	299												
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ttc act gaa cag ccc atc aca gat ttt tgt agt gta ata aga att aat Phe Thr Glu Gln Pro Ile Thr Asp Phe Cys Ser Val Ile Arg Ile Asn 95 100 105 110	395												
tcc act gct cca ttt gaa gaa caa gag aat tat ttt ttg tta tgt gac Ser Thr Ala Pro Phe Glu Glu Glu Glu Asn Tyr Phe Leu Leu Cys Asp 115 120 125	443												
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Lys	Lys	Leu	Asp 210	Asn	Leu	Gln	Cys	Leu 215	Tyr	Cys	Glu	Lys	Thr 220	Phe	Arg	
_						gat Asp		_				_		-	_	779
			-		_	gaa Glu 245		-	-			-				827
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	_	-	-		_	gaa Glu	-	~			-		_	_		923
	-		-	-	_	tta Leu		_	-	_		_	-			971
	_	_		_		atg Met		_	_		_		_			1019
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		_				aaa Lys	_	_		_			_	_	_	1163
						ctc Leu										1211
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435

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atg gag gcg ctg aac acg gcg cag ggc gcg gac ttc atc tac agc
Met Glu Ala Leu Asn Thr Ala Gln Gly Ala Arg Asp Phe Ile Tyr Ser
1 5 10 15

ctg cac tcc acg gag agg agc tgc ctg ctc aaa gag ctg cac cgc ttc Leu His Ser Thr Glu Arg Ser Cys Leu Leu Lys Glu Leu His Arg Phe $20 \hspace{1cm} 25 \hspace{1cm} 30$

gag tot att gcc att gcc caa gaa aaa ttg gaa gct cca ccc acc
Glu Ser Ile Ala Ile Ala Gln Glu Lys Leu Glu Ala Pro Pro Pro Thr
35 40 45

cca gga cag ctg aga tat gta ttc atc cac aat gcg ata cct ttc ata

Pro Gly Gln Leu Arg Tyr Val Phe Ile His Asn Ala Ile Pro Phe Ile

50 55 60

ggg ttt ggc ttt ttg gat aat gca att atg att gtt gct gga acc cat

Gly Phe Gly Phe Leu Asp Asn Ala Ile Met Ile Val Ala Gly Thr His

65 70 75 80

att gaa atg tct att gga att att ttg gga att tca act atg gca gct

Ile Glu Met Ser Ile Gly Ile Ile Leu Gly Ile Ser Thr Met Ala Ala

85

90

95

gct gct ttg gga aat ctt gtg tca gat cta gct gga ctt gga ctt gca 394 Ala Ala Leu Gly Asn Leu Val Ser Asp Leu Ala Gly Leu Gly Leu Ala 100 105 110

ggc tac gtt gaa gca ttg gct tcc agg tta ggc ctg tca att cct gat

Gly Tyr Val Glu Ala Leu Ala Ser Arg Leu Gly Leu Ser Ile Pro Asp

115 120 125

490 ctc aca cca aag caa gtt gac atg tgg caa aca cgt ctt agt aca cat Leu Thr Pro Lys Gln Val Asp Met Trp Gln Thr Arg Leu Ser Thr His 130 135 ttg ggc aaa gct gtt ggg gtg act att ggc tgc att cta gga atg ttt 538 Leu Gly Lys Ala Val Gly Val Thr Ile Gly Cys Ile Leu Gly Met Phe 145 150 155 160 586 cct tta att ttc ttt gga gga ggt gaa gat gaa aaa ctg gaa acg Pro Leu Ile Phe Phe Gly Gly Glu Glu Asp Glu Lys Leu Glu Thr 165 aaa agt taa tcctctt agaataccta taaaaagatg taaactaatg tacctcagta 642 Lys Ser * attaaatatg ctgtcacaac atttaggaat taagacagta acagtataga tatgggatca 702 aataatttag catgtattat ggaaaacact aacttattgt ggcttgatct tcttaggaca 762 tettttttaa aaagetgttt agtateattt tgtgtatatt gttgaaatge ttttteatea 822 atagcagtca acattttatc ctttctttt atattcataa tgttatttaa gtgtcattga 882 tgtactgtat tgacttgggg tttgcttatt tgttacttaa catgtgtaca tgcatgaaag 942 catttttcgt tgttccctga tagttacatt tcaaccttgg gatttttcca aattacttaa 1002 gatgtttaat gtcagttaaa gattttttta ccctcttttt gggaacatca attttgtact 1062 gttatgcagt aaacatttat aataatataa aa 1094

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<211> 1046

<212> DNA

<213> Homo sapiens

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ggtaccagat tcagcccatt tggccccgac gcctctgttc tcggaatccg ggtgctgcgg 180
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Met Arg Phe Arg Val Ser Ser
1 5

				ggc Gly											34	40
	_		_	gat Asp		-		_	_	-	-		_		38	38
				tgc Cys 45											43	36
				ggg ggg											48	34
				ggt Gly						_					53	32
				ctt Leu			-			_					58	30
			-	ctc Leu									_		62	8 .
				ctc Leu 125											67	'6
_				 gag Glu	_	_	_			-	-		_	_	72	!4
				gtc Val											77	'2
				ctg Leu						-	-		_		82	:0
		_		 agc Ser		_			_			_	_	_	86	;8
_		-	-	aag Lys 205		_	_		-		-			_	91	.6
			_	tct Ser		-		_		-	-	_	_		96	4

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			atg Met													147
			att Ile													195
			cga Arg													243
			cga Arg					_		_	_				_	291
			cac His 95		-	-		-	_			-		_		339
			gcc Ala		_	_				_	-	_	_			387
			cac His													435

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		gcc Ala				_										579
		tcc Ser 190														627
		cac His														675
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		gaa Glu														771
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		ctt Leu			-						-					963
_		aaa Lys		-			-			_					_	1011
		tca Ser														1059
		aat Asn 350														1107

-					_	aac Asn 370				-			_	_		1155
				-	_	aag Lys	_			-					_	1203
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	_		_		-	tct Ser			_		_	-				1299
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_			_			gtt Val			-							1491
		-		-	-	gcc Ala			_	_		_	_			1539
_				~	_	gca Ala						_				1587
				_	_	aaa Lys 530	_									1635
_						agt Ser				_						1683
						tgg Trp										1731
_		_	-	-	_	tta Leu		-			_		-	-		1779
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Lys Ile Ala Gly Pro Arg Lys Glu Glu Val Trp Asp Ser Phe Lys Val 590 595 600

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gacgaagaca acgacagcga cggctacgcc gaagcactcg ttccgggggt gaagcctcct	180
gcgccggcct tgcctcggat ccaggatgag aagactgata aaagaagaag ctagctgaac	240
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aat tot gac agt gac agc aat atg gta gag aaa cca tat gga aga aag Asn Ser Asp Ser Asp Ser Asn Met Val Glu Lys Pro Tyr Gly Arg Lys 15 20 25	336
agt aaa gac aag att gca tcc tac agc aaa act cca aaa att gaa cga Ser Lys Asp Lys Ile Ala Ser Tyr Ser Lys Thr Pro Lys Ile Glu Arg 30 35 40 45	384
agt gat gtg agc aag gag atg aaa gag aaa tca tcc atg aaa cgt aaa Ser Asp Val Ser Lys Glu Met Lys Glu Lys Ser Ser Met Lys Arg Lys 50 55 60	432
ctt cct ttt act att agc cca tca aga aat gaa gaa cga gat tca gac Leu Pro Phe Thr Ile Ser Pro Ser Arg Asn Glu Glu Arg Asp Ser Asp 65 70 75	480
aca gag aaa gaa ggt cca gaa aag aag aag aca aaa aag gaa gct gga Thr Glu Lys Glu Gly Pro Glu Lys Lys Lys Thr Lys Lys Glu Ala Gly 80 85 90	528
aat aag aaa tcc aca cca gtt agc att ctt ttt ggt tat cca ctc tct Asn Lys Lys Ser Thr Pro Val Ser Ile Leu Phe Gly Tyr Pro Leu Ser 95 100 105	576
gag cga aaa cag atg gca ctt ctt atg cag atg aca gca aga gac aac Glu Arg Lys Gln Met Ala Leu Leu Met Gln Met Thr Ala Arg Asp Asn 110 125	624
agt cca gat tcc aca cca aat cat cca tca caa aca ac	672
aag aaa act ccc agt tct tca tct cga cag aaa gat aaa gtt aat aaa Lys Lys Thr Pro Ser Ser Ser Ser Arg Gln Lys Asp Lys Val Asn Lys 145 150 155	720
aga aat gaa cgt ggt gaa act cct tta cac atg gct gct att cga gga Arg Asn Glu Arg Gly Glu Thr Pro Leu His Met Ala Ala Ile Arg Gly 160 165 170	768
gat gtg aaa caa gtt aaa gaa tta ata agt tta ggg gca aat gtg aat	816

Asp	Val 175	Lys	Gln	Val	Lys	Glu 180	Leu	Ile	Ser	Leu	Gly 185	Ala	Asn	Val	Asn	
		-		-					-		gaa Glu	-	-		_	864
			-	-	_	_				-	gct Ala		-	-	_	912
					_	_	_				cat His	_		_	_	960
-			_	-		-	_	_			cgt Arg			~ ~		1008
											gtg Val 265					1056
			_		_				-		gtg Val				•	1104
											caa Gln					1152
											gag Glu					1200
	_	_	_		_				_		aca Thr					1248
											gat Asp 345					1296
											gaa Glu		_		_	1344
											gca Ala					1392
											caa Gln					1440
											gaa Glu					1488

405 410 400 aaa aag att tot act toa tgt too gto atc cot gaa aca toa aat tot 1536 Lys Lys Ile Ser Thr Ser Cys Ser Val Ile Pro Glu Thr Ser Asn Ser gat atg caa acc aaa aag gaa tat gta gtt tca ggt gaa cac aaa cag 1584 Asp Met Gln Thr Lys Lys Glu Tyr Val Val Ser Gly Glu His Lys Gln 435 440 aaa ggc aaa gtt aaa aga aaa ttg aaa aat cag aat aaa aat aaa gag 1632 Lys Gly Lys Val Lys Arg Lys Leu Lys Asn Gln Asn Lys Asn Lys Glu 450 455 aac caa gag cta aag caa gaa aag gaa gga aaa gaa aat aca aga ata 1680 Asn Gln Glu Leu Lys Gln Glu Lys Glu Gly Lys Glu Asn Thr Arg Ile 465 470 aca aac ttg aca gta aat act gga cta gat tgt tca gaa aag acc aga 1728 Thr Asn Leu Thr Val Asn Thr Gly Leu Asp Cys Ser Glu Lys Thr Arg 480 485 gag gag ggg aac ttt agg aaa tct ttt agc cca aaa gat gat act tca 1776 Glu Glu Gly Asn Phe Arg Lys Ser Phe Ser Pro Lys Asp Asp Thr Ser 495 500 tta cat tta ttt cat att tcc act ggt aaa tct ccc aaa cat tct tgt 1824 Leu His Leu Phe His Ile Ser Thr Gly Lys Ser Pro Lys His Ser Cys 515 gga tta agt gaa aaa cag tca aca cca cta aaa caa gaa cat act aaa 1872 Gly Leu Ser Glu Lys Gln Ser Thr Pro Leu Lys Gln Glu His Thr Lys 1920 aca tgt tta tca cca gga agt tct gaa atg tca tta cag cct gat ctt Thr Cys Leu Ser Pro Gly Ser Ser Glu Met Ser Leu Gln Pro Asp Leu 545 550 1968 gtt cgg tat gat aat aca gaa tct gaa ttc ttg cca gaa agt tca agt Val Arg Tyr Asp Asn Thr Glu Ser Glu Phe Leu Pro Glu Ser Ser Ser 560 565 gta aaa tct tgt aag cat aag gaa aaa agc aaa cat cag aaa gat ttc 2016 Val Lys Ser Cys Lys His Lys Glu Lys Ser Lys His Gln Lys Asp Phe 575 2064 cac tta gaa ttt ggt gaa aaa tca aat gcc aaa ata aag gat gaa gat His Leu Glu Phe Gly Glu Lys Ser Asn Ala Lys Ile Lys Asp Glu Asp 590 cat agt cca aca ttt gaa aat tca gat tgc aca ctg aaa aaa atg gat 2112 His Ser Pro Thr Phe Glu Asn Ser Asp Cys Thr Leu Lys Lys Met Asp 610 615 aaa gaa ggt aaa aca tta aaa aaa cat aaa ttg aag cat aaa gag agg 2160 Lys Glu Gly Lys Thr Leu Lys Lys His Lys Leu Lys His Lys Glu Arg 625 630

gaa a Glu L		u Lys				-		_		_	_	_			2208
aaa a Lys T 6!			_	_		-	-	-		_		_		_	2256
aga ga Arg Gi 670									_	_	_		_	_	2304
ctc ti Leu Pl			_	_		_					-				2352
aaa tt Lys Le			Asn			_	_				_	_	_		2400
gtg to Val Se		s Glu						_	_	_	-			-	2448
gaa ag Glu Se 73															2496
gag ag Glu Ar 750														_	2544
ggt at Gly Me													_	-	2592
gaa at Glu Il	_		Glu			_	_			_	_				2640
aaa aa Lys Ly		s Gly		_		-	agta	itccc	tc g	ıaggg	igaac	a ag	gctta	ıcgcg	2694
taccca	agctt	tctt	gtaca	aa ag	gtggt	ccct	ata	ıgtga	.gtc	gtat	tata	ag c	tggc	gcctg	2754
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cc	gggcg	gag	gaga	gctc	aa g	ctaa	gggt	g at	cagc	ccat	gac	ctaa	acc	tcca	gacaaa	120
at	aaaac	gga .	aaat	ttgc	ta g	aatc	aaga	Me				э Су			t gga l Gly	173
_	c cag l Gln 10		-					-							_	221
	c aca s Thr 5												-	-		269
	a ctt u Leu															317
	c ttt s Phe								-	_			_		_	365
	g tca s Ser	-	~	_						_			_			413
	t ttg n Leu 90				-		_	_	_			_	_	_		461
	t gga e Gly 5													_		509
	g ata n Ile															557
_	g aaa g Lys				_		_		_		_	_				605
ca	a ttt	acg	aat	cca	gga	agg	caa	act	gaa	ttt	gct	cca	gaa	act	ggt	653

Gln Phe Thr Asn Pro Gly Arg Gln Thr Glu Phe Ala Pro Glu Thr Gly 155 160 165	
aaa aga gaa aaa aga agg ctt aca aaa aat gca acc gct ggt tca gac Lys Arg Glu Lys Arg Arg Leu Thr Lys Asn Ala Thr Ala Gly Ser Asp 170 175 180	701
aga caa gtg ata cca gca aag agt aag gtc tat gat agc cag ggt ctc Arg Gln Val Ile Pro Ala Lys Ser Lys Val Tyr Asp Ser Gln Gly Leu 185 190 195 200	749
ctg att ttt agt ggg atg gac ctc tgt gac tgc ctg gat gaa gac tgc Leu Ile Phe Ser Gly Met Asp Leu Cys Asp Cys Leu Asp Glu Asp Cys 205 210 215	797
tta gga tgt ttc tat gct tgt cct gcc tgt ggt tct acc aag tgt gga Leu Gly Cys Phe Tyr Ala Cys Pro Ala Cys Gly Ser Thr Lys Cys Gly 220 225 230	845
gct gaa tgc cgc tgt gac cgc aag tgg ctg tat gag caa att gaa att Ala Glu Cys Arg Cys Asp Arg Lys Trp Leu Tyr Glu Gln Ile Glu Ile 235 240 245	893
gaa gga gga gaa ata att cat aat aaa cat gct gga taa tctgcggtac Glu Gly Gly Glu Ile Ile His Asn Lys His Ala Gly * 250 255 260	942
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aac gga att agc agt gga tta gcc cca gga cag ccg ttt ccg agt agc Asn Gly Ile Ser Ser Gly Leu Ala Pro Gly Gln Pro Phe Pro Ser Ser 45 50 55	1154
cag ggt tct ctc tgc att agt ggg act gag gag cca gag aag acc ctg Gln Gly Ser Leu Cys Ile Ser Gly Thr Glu Glu Pro Glu Lys Thr Leu 60 65 70 75	1202
aga gct aac cct gag ttg tgc ggt tct ctg cac ctg aac ggg agt cca Arg Ala Asn Pro Glu Leu Cys Gly Ser Leu His Leu Asn Gly Ser Pro 80 85 90	1250
agt agc tgc ata gcc agt agg cct tcc tgg gtg gaa gac att ggg gat Ser Ser Cys Ile Ala Ser Arg Pro Ser Trp Val Glu Asp Ile Gly Asp 95 100 105	1298
aac ctg tac tat gga cac tac cac ggg ttt ggg gac act gct gaa agc Asn Leu Tyr Tyr Gly His Tyr His Gly Phe Gly Asp Thr Ala Glu Ser 110 115 120	1346
atc cca gaa ctg aac agt gtg gtc gag cat tcc aag tcc gtg aag gtg Ile Pro Glu Leu Asn Ser Val Val Glu His Ser Lys Ser Val Lys Val 125 130 135	1394
cag gag cgg tac gac agt gcc gtg ctg ggc acc atg cac ctg cac cac Gln Glu Arg Tyr Asp Ser Ala Val Leu Gly Thr Met His Leu His His 140 145 150 155	1442
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aag cat tac cac tta aag agg aac cag agc ttc tgc cca act gtc aac
Lys His Tyr His Leu Lys Arg Asn Gln Ser Phe Cys Pro Thr Val Asn
70 75 80

atc aac ttc gac aaa tac cac cca ggc tac ttt ggg aaa gtt ggt atg

Ile Asn Phe Asp Lys Tyr His Pro Gly Tyr Phe Gly Lys Val Gly Met

60

ctt gac aaa ttg tgg act ttg gtc agt gaa cag aca cgg gtg aat gct 582

486

Leu Asp Lys Leu Trp Thr Leu Val Ser Glu Gln Thr Arg Val Asn Ala 85 90 95	
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ggc tac tat aaa gtt ctg gga aag gga aag ctc cca aag cag cct gtc Gly Tyr Tyr Lys Val Leu Gly Lys Gly Lys Leu Pro Lys Gln Pro Val 120 125 130	678
atc gtg aag gcc aaa ttc ttc agc aga aga gct gag gag aag att aag Ile Val Lys Ala Lys Phe Phe Ser Arg Arg Ala Glu Glu Lys Ile Lys 135 140 145	726
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aca aag gac aaa gaa agc cta aac ttt cct ttt ttc tgg gct cca a Thr Lys Asp Lys Glu Ser Leu Asn Phe Pro Phe Phe Trp Ala Pro I 15 20 25	
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gtt gct ata aat ttc ctg ctt ctc aaa tat ctg gat ttt tgg cta cc Val Ala Ile Asn Phe Leu Leu Leu Lys Tyr Leu Asp Phe Trp Leu Pi 60 65 70	
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Lys Arg Lys Asn Ser Asn Val Asp Ser Ser Tyr Leu Glu Ser Leu 90 95 100	
caa tcc tgt ccg agg gga gtt gtg cca ttt cag gcg ggc tca cgg Gln Ser Cys Pro Arg Gly Val Val Pro Phe Gln Ala Gly Ser Arg 105 110 115	
tat gag ctg agt ttc caa ggg atg att cag aca aac ata gct tcc Tyr Glu Leu Ser Phe Gln Gly Met Ile Gln Thr Asn Ile Ala Ser 120 125 130	
act caa aag gat gtc atc aga aga cca aca ttt gtg cct cag tgg Thr Gln Lys Asp Val Ile Arg Arg Pro Thr Phe Val Pro Gln Trp 140 145 150	Tyr
gtg cag cag atg aag aga ggg cca gag taa g tgttctgaag cagctg Val Gln Gln Met Lys Arg Gly Pro Glu * 155 160	tttg 1194
ctgacagatg cttgagatgt tcatgccctg ggctcatcaa gtcactcgtg aatc	tggagc 1254
ctgttttcct gaaaagttcc tgtttgcatt actctgcagt ttccatttgc atta	tcgatg 1314
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attttgtcct gtgtccttac cggcaaaacg atgtataaat gaaagaaatt gaga	tggtgc 240

300

360

420

477

Met Tyr Arg

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atccttctgg tttgccacat atgcatgctg tcaggaagtt gatgaggt atg tac agg

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cat ctg ct His Leu Le 20							573
agc cgc ca Ser Arg Gl	•			aatct ct	ttccccat t	caccccacc	625
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<220>

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Met Ala Leu Asp Gly
1 5

ata agg atg cca gat ggc tgc tac gcg gac ggg acg tgg gaa ctg agt

Ile Arg Met Pro Asp Gly Cys Tyr Ala Asp Gly Thr Trp Glu Leu Ser

10 15 20

						aac Asn										270
						gtg Val			-						_	318
						gac Asp 60										366
			-	_		cat His				_	-				-	414
_	_	-	-		_	ttc Phe			_			_		_	_	462
				_	_	tat Tyr		_							-	510
						tct Ser			-						_	558
						ctc Leu 140										606
						gat Asp					-		-		_	654
	-					act Thr					_				-	702
						aca Thr						_	_		_	750
						act Thr										798
	_					ata Ile 220		_	_	_				_		846
						atg Met		_			-			-		894
gca	aaa	atc	aac	caa	gga	tgg	ctt	gat	tcc	tca	aga	tct	ctc	atg	gaa	942

Ala	Lys	Ile	Asn	Gln 250	Gly	Trp	Leu	Asp	Ser 255	Ser	Arg	Ser	Leu	Met 260	Glu	
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					aat Asn											1038
					aaa Lys		_			_	_			_	_	1086
					atg Met 315											1134
					aca Thr								_	_		1182
					gat Asp											1230
					tca Ser											1278
					att Ile											1326
					tat Tyr 395											1374
					gaa Glu											1422
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					ctc Leu											1518
					gac Asp											1566
					tcc Ser											1614

470	475	480	485
Asn Leu Glu Val G		cc ttt ctg aag atg c er Phe Leu Lys Met (495	
	n Leu Ile Pro G	ag cag atc acg act of lu Gln Ile Thr Thr A	
		at cta aaa aag tat a yr Leu Lys Lys Tyr I 530	
		cc cat cag aat gta g la His Gln Asn Val <i>F</i> 545	
		tt att caa gct tgg c he Ile Gln Ala Trp G 560	
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		ca tgg cgt ttc agc a nr Trp Arg Phe Ser A 610	
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gat gaa gta cga tt Asp Glu Val Arg Le 630	g tcc ttc att to u Ser Phe Ile Cy 635	gt act gaa gta gat t ys Thr Glu Val Asp C 640	gc aaa gtg 2094 ys Lys Val 645
	e Gly Gly Tyr Il	ta ttt ctc tca aca c Le Phe Leu Ser Thr A 655	
		ag atg ttc tac aaa c Lu Met Phe Tyr Lys L 70 6	
ggt tgg gtg tga at Gly Trp Val * 680	a gaaatactgt tta	aatgaaac tccacggcca	taacaatatt 2245
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Ala Val Ile Asp Ser Ile Phe Val Trp Phe Ile Phe Ile Ser Leu Ala
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Met Glu Val Val Asp Glu

1 5

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Thr Glu Ala Leu Gln Arg Phe Phe Glu Gly His Asp Ile Asn Gly Ala

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Leu Glu Pro Ser Asn Ile Asp Thr Ser Ile Leu Glu Glu Tyr Ile Ser
25 30 35

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Lys Glu Asp Ala Ser Asp Leu Cys Phe Pro Asp Ile Ser Ala Pro Ala
40
45
50

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Ser Ser Ala Ser Tyr Ser His Gly Gln Pro Ala Met Pro Gly Ser Ser

55 60 65 70

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				cca Pro		_										403
				atg Met												451
				aag Lys	-			_	_							499
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				ccc Pro 155												595
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_	-			aat Asn												931
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cca	CCC	tgg	cct	CCC	cag	ggt	ccg	ctc	tcc	ccg	ggc	cct	ggt	tcc	ttg	1027

Pro Pro Trp Pro Pro Gln Gly Pro Leu Ser Pro Gly Pro Gly Ser Leu 300 305 cct ctc agc att gcc cgt gtc cag aca ccg cct tgg cac ccg cca ggt 1075 Pro Leu Ser Ile Ala Arg Val Gln Thr Pro Pro Trp His Pro Pro Gly 315 gcc ccc tcc cca ggc ctc ctg cag gac agt gac agc ctc agt ggc tcc 1123 Ala Pro Ser Pro Gly Leu Leu Gln Asp Ser Asp Ser Leu Ser Gly Ser 330 tac ctg gac ccc aac tac cag tcc atc aag tgg cag cct cat cag cag 1171 Tyr Leu Asp Pro Asn Tyr Gln Ser Ile Lys Trp Gln Pro His Gln Gln 345 350 aac aag tgg gcg acc ctg tac gat gct aac tac aag gag ctg ccc atg 1219 Asn Lys Trp Ala Thr Leu Tyr Asp Ala Asn Tyr Lys Glu Leu Pro Met 1267 ctc acc tac cgc gtg gat gcg gac aag ggc ttc aac ttt tcg gtg ggc Leu Thr Tyr Arg Val Asp Ala Asp Lys Gly Phe Asn Phe Ser Val Gly 375 380 385 gac gac gcc ttt gtg tgc cag aag aag aac cac ttc cag gtg aca gtg 1315 Asp Asp Ala Phe Val Cys Gln Lys Lys Asn His Phe Gln Val Thr Val 395 400 tac atc ggc atg ctg ggc gag ccc aag tac gtc aag acg ccc gag ggc 1363 Tyr Ile Gly Met Leu Gly Glu Pro Lys Tyr Val Lys Thr Pro Glu Gly 410 ctc aag ccc ctc gac tgc ttc tat ctg aag ctg cac gga gtg aag ctg 1411 Leu Lys Pro Leu Asp Cys Phe Tyr Leu Lys Leu His Gly Val Lys Leu 425 gag gcc ctg aac cag tcc att aac atc gag cag tcc cag tca gac cgg 1459 Glu Ala Leu Asn Gln Ser Ile Asn Ile Glu Gln Ser Gln Ser Asp Arg 440 age aag egg eee tte aac eeg gte aeg gte aat etg eee eet gag eag 1507 Ser Lys Arg Pro Phe Asn Pro Val Thr Val Asn Leu Pro Pro Glu Gln 460 gtc acg aag gtg act gtg ggg cgg ctg cac ttc agc gag acc acc gct 1555 Val Thr Lys Val Thr Val Gly Arg Leu His Phe Ser Glu Thr Thr Ala 475 480 aac aac atg cgt aag aag ggc aag ccc aac ccg gac cag agg tac ttc 1603 Asn Asn Met Arg Lys Lys Gly Lys Pro Asn Pro Asp Gln Arg Tyr Phe 490 495 atg ctg gtg gcc ctc cag gct cat gca cag aac cag aac tac acg 1651 Met Leu Val Val Ala Leu Gln Ala His Ala Gln Asn Gln Asn Tyr Thr 505 510 515 ctg gcc gcc cag atc tca gag cgc atc att gtg cgg gcc tcc aac cca 1699 Leu Ala Ala Gln Ile Ser Glu Arg Ile Ile Val Arg Ala Ser Asn Pro

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		gac Asp									1891
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											ggc Gly					691
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190 195 200

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gaa ccc acg ctt ctg acc tgt gct ctg tct ttg cag ttc tgc acg gag 154 Glu Pro Thr Leu Leu Thr Cys Ala Leu Ser Leu Gln Phe Cys Thr Glu

202 cta aac cag ccg acc ctg ccc aac atc cgc aag tgg aag ggg ccc cgg Leu Asn Gln Pro Thr Leu Pro Asn Ile Arg Lys Trp Lys Gly Pro Arg

35 40 gga tgc tgg aag gct gtt gtt gct gag aag ccc tcg aat cag ctc cag 250 Gly Cys Trp Lys Ala Val Val Ala Glu Lys Pro Ser Asn Gln Leu Gln

55

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		_	-	ttt aaa tcc ttg Phe Lys Ser Leu 110	
	-			ttt aga ttg gta Phe Arg Leu Val 125	-
	Gln Glu G			gtg ttg gga gag Val Leu Gly Glu	
				ctt tgt cct tct Leu Cys Pro Ser 160	
				gtg cag agc tca Val Gln Ser Ser 175	
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tcc cct gtg Ser Pro Val								876
tac tca tca Tyr Ser Ser 35	Leu Arg I	Phe Ala H						924
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Met Thr Val Glu Leu Trp Leu Arg Leu Arg Gly Lys Gly Leu

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<220>

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			-	_	atg Met	_			_			_			-	948
_	_			_	gtt Val		_	_	-	_		-	-			996
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					gtg Val											1188
_					cct Pro	_			-		_				_	1236
					gag Glu 195											1284
					ttg Leu											1332
					tac Tyr		_	_			_	_			-	1380
	-		_	_	cac His			-	-			_			-	1428
					att Ile	_		_		_	_		_	_	_	1476
_		-	_		aaa Lys 275							_		-		1524

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gct ctg aaa atg gat ttt tct cta ccc cct tct act tac gcc acc atg Ala Leu Lys Met Asp Phe Ser Leu Pro Pro Ser Thr Tyr Ala Thr Met 305 310 315	1620
gcc att cga gaa gtg cta aaa atg gat acc agt atc aag aac cag acg Ala Ile Arg Glu Val Leu Lys Met Asp Thr Ser Ile Lys Asn Gln Thr 320 325 330	1668
cag ctg aat aca acc tgg ctt cgc tga gcagt accttgtcca cagattagaa Gln Leu Asn Thr Thr Trp Leu Arg * 335 340	1720
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acc gcc cgg cac gca cct gcg Thr Ala Arg His Ala Pro Ala 60			243								
ttg ctt aag gat gta aag att Leu Leu Lys Asp Val Lys Ile 75 80	Ser Val Ser Phe		291								
agt aag gac agg aag gtg ctg Ser Lys Asp Arg Lys Val Leu 90 95			339								
gcg gag tgc ggt ctg ctc ctt Ala Glu Cys Gly Leu Leu Leu 110			387								
tgt ccc ttt ggc ggg agt gtt Cys Pro Phe Gly Gly Ser Val 125			435								
agt gct gat aag aag gat gag Ser Ala Asp Lys Lys Asp Glu 140			483								
gtg gag tat gca gtg ctc gat Val Glu Tyr Ala Val Leu Asp 155 160	Glu Leu Glu Asp		531								

gag c Glu I 170																	579
cag a Gln A																	627
tgt t Cys I							ag g	ggcto	cttag	gc aa	aaac	ccaa	a gaq	gagat	ttg		680
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gaa cag cct caa gtg gtg gtt tta Glu Gln Pro Gln Val Val Val Leu 55 60									
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75 80 85	
gaa cca act cca gcc gat gga aga atc ata tat cga aaa cca gtc aag Glu Pro Thr Pro Ala Asp Gly Arg Ile Ile Tyr Arg Lys Pro Val Lys 90 95 100	343
cat ccc tca gat gaa aaa tat tca ggt tta aca gca agc tca aaa aag His Pro Ser Asp Glu Lys Tyr Ser Gly Leu Thr Ala Ser Ser Lys Lys 105 110 115	391
aag aag cca aat gaa gat gaa gta aat cag gac tcg gtc aaa aag aac Lys Lys Pro Asn Glu Asp Glu Val Asn Gln Asp Ser Val Lys Lys Asn 120 125 130	439
tca caa aaa caa att aaa aat agt agc ctc ctt tct ttt gac aac gaa Ser Gln Lys Gln Ile Lys Asn Ser Ser Leu Leu Ser Phe Asp Asn Glu 135 140 145 150	487
gat gaa aat gag taa gtgtaaatat tttgaattta gtctactttg aaagtatatg Asp Glu Asn Glu * 155	542
gagtgttcat taaaatcaca ttttttccta ttataaagat actacaagtt ctttatagaa	602
agtttaggaa atagagaaaa aaatttaata aactacatct attcatcaat acccctctga	662
cttaaaatgc caactctata gaaattagct agtattaaca ttttgttatt tcccttgtgt	722
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aaa gat gcg cag atg aga gca gcg att aac caa aag ttg ata gaa act Lys Asp Ala Gln Met Arg Ala Ala Ile Asn Gln Lys Leu Ile Glu Thr 10 15 20	220

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gaa aaa gga cta gaa cac gtt act gtt gat gac ttg gtg gct gaa atc Glu Lys Gly Leu Glu His Val Thr Val Asp Asp Leu Val Ala Glu Ile 60 65 70	364
act cca aaa ggc aga gcc ctg gta cct gac agt gta aag aag gag ctc Thr Pro Lys Gly Arg Ala Leu Val Pro Asp Ser Val Lys Lys Glu Leu 75 80 85	412
cta caa aga ata aga aca ttc ctt gct cag cat gcc agc ctt taa gat Leu Gln Arg Ile Arg Thr Phe Leu Ala Gln His Ala Ser Leu * 90 95 100	460
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	240
aattagaatc ttttcacatg agactacaga gaaagatttg tatttgtaac aaaaaattag	240 300
aattagaatc ttttcacatg agactacaga gaaagatttg tatttgtaac aaaaaattag ctgggcatgg tggcaggtgc ctgtaatccc agctacttgg gaggctgagg caggagaatc	240 300 360

Thr	Gly	Ile	Leu 20	Lys	Gly	Val	Asn	Leu 25	Gln	Arg	Lys	Gln	Ala 30	Ala	Asn	
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		ggc Gly														668
		gtg Val														716
		tgc Cys														764
_		acc Thr														812
		aag Lys 115														860
		cct Pro			_		_	-		_		_				908
		gcc Ala														956
_		tct Ser														1004
		gac Asp														1052
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		gag Glu					-	_								1196
		att Ile														1244

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-	-	_	-	_	agg Arg												1388
		_	_		ctc Leu 310	_			_		-			_			1436
					gag Glu												1484
_				_	gac Asp				_	_			_				1532
					cgg Arg												1580
•			_	_	cgg Arg	_	_	_	_						_		1628
ccc Pro 385	tga *	cgc	ccct	gtg (cca	ctttg	gt aa	aataa	aacto	g ctg	gaaca	accc	aaaa	aaaa	aaa	,	1684
aaa																	1687
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250

245

255

60

117

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					Gly											165	
		_			gct Ala 25	-	_		_	-	-		_			213	
					ttc Phe											261	
_	_	_		_	gag Glu											309	
					tcc Ser											357	
					ctg Leu											405	
_	_	_		-	ggc Gly 105											453	
_	~		_	_	aaa Lys			-		_	_	-	-		_	501	
					cac His											549	
		-			cga Arg											597	
					ctg Leu											645	
					aat Asn 185											693	
					aca Thr											741	
	cac His	_		tga *	ggca	aggg	gat t	igato	ccctg	ga co	ctcc	cttct	aco	cca	cttc	796	

856 cctacacaat tctcttattt atttggtttg gctcctgttc caatttgaaa ggagtctgtg ttcataatac tgtttctcct ctcaatttcc cagaaattgg gttctatgct ggctggaaat 916 976 gttgggggaa agagaaggca aaggatgtgg aaatgagatg tgcttaggaa agggtcaggc ccatcgtagg agcaccatat gcctgcagcc ttttcactac gaattagaat aaggactatg 1036 1096 tggttgtctc tggaccttat caagacacct tagtgtctga ccaggggacg atagtaactt ttctaaggat tgaataaatt gagettttet tetggeacag aggtaetgag tggtaagtaa 1156 1216 cttttaccct gcctgagatt cctcaggaga aaaggcaacc tgcctccagc ctgaaataca taaagcctca ttttaagact gtaagtccat gctgcctggc tactagagag caaggggctt 1276 1336 tottaccaco agtgotgagg agaaaagtac tgaacggaaa cggagttgto titgtactot 1396 tgagttgtac cttattcttc cacttggcct gagtttttat aaaatttcaa taaattgtga 1416 cagtgtgaaa aaaaaaaaaa

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Pro Ala Met Val Asn Pro Thr Met Phe Phe His Ile Ala Val Asp Gly 25 30 35	
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cag agt ggt gac ttc aca cgc cat aca gca ttg gtg gca agt cca tct Gln Ser Gly Asp Phe Thr Arg His Thr Ala Leu Val Ala Ser Pro Ser 90 95 100	700
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270 gtg tgt gcc aag tgt ggc tat gag ctg ttc tcc agc cgc tcg aag tat Val Cys Ala Lys Cys Gly Tyr Glu Leu Phe Ser Ser Arg Ser Lys Tyr 30 318 gca cac tcg tct cca tgg ccg gcg ttc acc gag acc att cac gcc gac Ala His Ser Ser Pro Trp Pro Ala Phe Thr Glu Thr Ile His Ala Asp 40 45 50 agc gtg gcc aag cgt ccg gag cac aat aga tct gaa gcc ttg aag gtg 366 Ser Val Ala Lys Arg Pro Glu His Asn Arg Ser Glu Ala Leu Lys Val 55 414 tcc tgt ggc aag tgt ggc aat ggg ttg ggc cac gag ttc ctg aac gac Ser Cys Gly Lys Cys Gly Asn Gly Leu Gly His Glu Phe Leu Asn Asp 465 qqc ccc aag ccg qgg cag tcc cga ttc tga a tattcagcag ctcgctgaag Gly Pro Lys Pro Gly Gln Ser Arg Phe 90 95 525 tttgtcccta aaggcaaaga aacttctgcc tcccagggtc actaggcggg cagcccacac 585 ccacccaga cggccaccac actgaggcca cacgttggcc attccacctt ggagttggaa ccctgggcgt cgagacagga aggcagggcg cagtggttga aacatcagga cactcccaag 645 705 gccccggctc tgaacaagac cttttcgttt cttggaaaag agactcattt gctgatggtt catgccttct gctgggacag gcctgggctg tgcagccaca ctgtcggctg acttagcccc 765 825 ctgctcactc taggtgcctc caggaggtga gccctgggtg cagctggtct ctgaatgacg 885 ttacaccctc accttctttt cctggccctg tctctgggac tctcccctgt gaggcccaat 945 tccaagacag actctcgtcc tcaccgaagc ttaggcccac atctcccagg ctgcttagga 1005 gacagaatgg aaacggaggc cgccctgcc agccgccctg gccctggtca ctgcatgatc 1065 cgctctggtc aaacccttcc aggccagcca gagtggggat ggtctgtgac ctgctgggaa 1125 ggcaggctga tggggcacac ccttggcctc tcgtccacga ggggagaaac ctaaaccctg tttcacaatc tgtgcggaag tagcttgcct cacttctgct taggaaagcg gctgttgctc 1185 cataactcta accagcacag ggctgaggcc tgcagtgcac acctgcaggg aggcccttcc 1245 caaggtqtqq tgactqtgcc ttactgtaca tgctcggagg cctggccata taggagggtg 1305 ggtgatgctg aaatcacccc ccatcttaag taattacttt ctggagtaat caggtggaaa 1365 1379 tccatagaca aatg

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	175					180					185					
_			-											ctg Leu		684
-		-	_											cga Arg 220		732
-			_	_	_	_								cat His		780
-	-	_		_		_	-		_		_	_		tta Leu	_	828
_									_		_		-	gga Gly		876
_	_				-			_		_	-			cct Pro		924
														gga Gly 300		972
														tct Ser		1020
														caa Gln		1068
														agc Ser		1116
-	-			_			_	_		_	_			gtg Val		1164
														gct Ala 380		1212
														gcc Ala		1260
														ggc Gly		1308

														ccc Pro		1356
														cag Gln		1404
														gaa Glu 460		1452
														aca Thr		1500
														gaa Glu		1548
														ttt Phe		1596
														aag Lys		1644
_		_												gtt Val 540		1692
														aat Asn		1740
														aag Lys		1788
			_		ctc Leu							taa *	tcad	caga	cct	1837
cag	gggct	ccc a	aacag	gggag	ga aa	aaaa	caato	c act	tggt	cttg	tcta	ataag	gtc a	actc	tgcttt	1897
atc	ttgct	caa a	agaca	aatti	t to	caago	caato	c ctt	tagt	ttt	agt	ttc	tgg a	aatag	gctagt	1957
att	gggti	ctt d	ctagi	tttt	ct ca	accti	ttag	g ttt	ttad	ctct	aatt	ttg	taa (ccat	gtatat	2017
gct	agcag	gtc (cacti	tctad	cg co	cacca	accca	a aat	gggt	cag	acco	cttga	aag a	aaac	gtcact	2077
tca	aacto	cag a	aatga	aaati	tt to	catta	aatat	t taa	aatt	gtg	aago	caaag	ggt (caata	aggctt	2137
ata	tttaa	att a	aaago	cctta	ac to	gaaaa	ataag	g aaa	atga	gctt	ag					2179

<210> 118

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	125	130		135
			ctt gtg tct gag Leu Val Ser Glu 150	
	Gln Thr Glu		ttt gat atc ttc Phe Asp Ile Phe 165	
			cag gcg gaa ctc Gln Ala Glu Leu 180	
			ggg gta gac atg Gly Val Asp Met 195	
			ctt gga ctg acc Leu Gly Leu Thr	
			ata ggc tta ttc Ile Gly Leu Phe 230	
	Lys Met Asp 1		agc aaa ttg aca Ser Lys Leu Thr 245	_
			caa gag cac acg Gln Glu His Thr 260	
			cac ctt tgg aag His Leu Trp Lys 275	
			acg cca gga aac Thr Pro Gly Asn	
_	_		tct cgc ttc aga Ser Arg Phe Arg 310	
	Tyr Gln Ala 7		tcc agg tta cga Ser Arg Leu Arg 325	
=			tat cca tcc cgg Tyr Pro Ser Arg 340	
_			gca gcc cag ctc Ala Ala Gln Leu 355	

aaa aca aat cca gaa gtc cat aat tac cag cct caa tat cat cct aat Lys Thr Asn Pro Glu Val His Asn Tyr Gln Pro Gln Tyr His Pro Asn 365 370 375	1457
atc cat ccc agc cag ccc cgg tgg cat cct cac tct cca aat gtc agg Ile His Pro Ser Gln Pro Arg Trp His Pro His Ser Pro Asn Val Arg 380 385 390	1505
cca tcc ttt cag gat gac agg tcg cat tgg aaa gca tcg gcc agt gga Pro Ser Phe Gln Asp Asp Arg Ser His Trp Lys Ala Ser Ala Ser Gly 395 400 405	1553
gat gac agc cat ttt gat tat gtc cac gac cag aac cag aag aac tta Asp Asp Ser His Phe Asp Tyr Val His Asp Gln Asn Gln Lys Asn Leu 410 415 420	1601
gga ggg atg caa agt atg atg tat cga gat aaa ctc atg act gca ctt Gly Gly Met Gln Ser Met Met Tyr Arg Asp Lys Leu Met Thr Ala Leu 425 430 435	1649
tga gaga ctgaagcatc tctcttccat tcaccttcat agtttcattg cattccatga *	1706
aaagtgtctt ggcctcagat ggatggatgt gtttggacga gtgtctttaa ggagtagtcc	1766
tgaaaggtgt ttttggtgtc catgtaaata tttgaagata aaaccactat agcttgtcat	1826
aatttactgt tgactgcatt ctcattaaaa tgaaggtaaa ggctcaggaa tcatattgat	1886
gttctgattt taaaattgga gtcaaagtct atgtttatca ttttactatg ttcctgatgt	1946
tctttgttat ttaattaatg ggagcaaata aaaccagaag agcttgggaa gattgctcag	2006
catatattcc tgtcgtagaa gttgagattg ctagggtcca gtttccctag tgtggcctgg	2066
acgagtcatt tccccttcat tgacctcatt ttccccatct gaaaagagag ggttggacta	2126
agtgatctcc aaggtccttt ccaactctaa aattctgcaa tttgttaaca tttcattttg	2186
tttaggttga ggacatacat tcaaactaat tttatcacaa ggaaaactgc aatacccact	2246
tccttgacag agttactcct ttcagaagct aaataaagta tataacttat tagatgttat	2306
atagatacag ggggactttg aatttcacat cttaaagcag ttgagctact ttgaatttaa	2366
gcagtcgtac taatcttaaa ttgcatagca tttgttttga tcgaatttgc tgctcaagta	2426
tgggaataat ttttaatgtc ttaatgattg gtgctgctaa cttgcgtgat ttcagaagac	2486
ataattgtga atacacactg tcagaattgg gggattggtt tttaccctag acttcactct	2546
taaaaagcaa cgtgcaatca agatcattta tggctcaaat gaaagcatat aaggttttct	2606
tgaagttgtg ccaaagcatt ctgtagagta ggatgagatg gttgttgccc tagtctgttg	2666

2726 gtagaaccag aaatcaatat gttgtctttt aggttaaagc ttgtaccaaa atatttattt 2786 ccccatttc aagccctgag tcaaacattt ttttctctta ataatagacc tgaaatgttt tattaqtatt tctqtqaaat caqttqattc ttgtgccatt tttgtatatg taattgtaat 2846 tttgcccatg ttaggccctc taaaaaatgt ttgacatcct ttgagatatt ttattactaa 2906 aatctgatct tttttggcta ctgcaaaaat ctattcagca agaaggtatc agctgcatac 2966 3026 cttgcacagt ggagctgact acctataaac tctccctaag gcatttgttt acaggtgtat 3086 tccattttag cagacgttct gatgctcagt gtatgtgctg catacaaata aatgtgttct gaatcttttc atcttattga tagcattttt acaaatgtgt ttccaaggaa taaagattat 3146 3168 tcttgcttta aaaaaaaaaa aa

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(222) (241)..(10)

<400> 119

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ttttctcggg acgggagagg ccgtgtagcg tcgccgttac tccgaggaga taccagtcgg

70 75 65 528 age egt ett tit gig gga aat ett eet eee gae ate aet gag gaa gaa Ser Arg Leu Phe Val Gly Asn Leu Pro Pro Asp Ile Thr Glu Glu Glu 85 576 atg agg aaa cta ttt gag aaa tat gga aag gca ggc gaa gtc ttc att Met Arg Lys Leu Phe Glu Lys Tyr Gly Lys Ala Gly Glu Val Phe Ile 100 105 624 cat aag gat aaa gga ttt ggc ttt atc cgc ttg gaa acc cga acc cta His Lys Asp Lys Gly Phe Gly Phe Ile Arg Leu Glu Thr Arg Thr Leu 120 115 672 gcg gag att gcc aaa gtg gag ctg gac aat atg cca ctc cgt gga aag Ala Glu Ile Ala Lys Val Glu Leu Asp Asn Met Pro Leu Arg Gly Lys 130 cag ctg cgt gtg cgc ttt gcc tgc cat agt gca tcc ctt aca gtt cga 720 Gln Leu Arg Val Arg Phe Ala Cys His Ser Ala Ser Leu Thr Val Arg 145 150 155 768 aac ctt cct cag tat gtg tcc aac gaa ctg ctg gaa gaa gcc ttt tct Asn Leu Pro Gln Tyr Val Ser Asn Glu Leu Leu Glu Glu Ala Phe Ser 160 165 gtg ttt ggc cag gta gag agg gct gta gtc att gtg gat gat cga gga 816 Val Phe Gly Gln Val Glu Arg Ala Val Val Ile Val Asp Asp Arg Gly 180 1.85 agg ccc tca gga aaa ggc att gtt gag ttc tca ggg aag cca gct gct 864 Arg Pro Ser Gly Lys Gly Ile Val Glu Phe Ser Gly Lys Pro Ala Ala 195 200 912 cgg aaa gct ctg gac aga tgc agt gaa ggc tcc ttc ctg cta acc aca Arg Lys Ala Leu Asp Arg Cys Ser Glu Gly Ser Phe Leu Leu Thr Thr 210 215 ttt cct cgt cct gtg act gtg gag ccc atg gac cag tta gat gaa 960 Phe Pro Arg Pro Val Thr Val Glu Pro Met Asp Gln Leu Asp Asp Glu 225 230 gag gga ctt cca gag aag ctg gtt ata aaa aac cag caa ttt cac aag 1008 Glu Gly Leu Pro Glu Lys Leu Val Ile Lys Asn Gln Gln Phe His Lys 240 1056 gaa cga gag cag cca ccc aga ttt gca cag cct ggc tcc ttt gag tat Glu Arg Glu Gln Pro Pro Arg Phe Ala Gln Pro Gly Ser Phe Glu Tyr 255 1104 gaa tat gcc atg cgc tgg aag gca ctc att gag atg gag aag cag cag Glu Tyr Ala Met Arg Trp Lys Ala Leu Ile Glu Met Glu Lys Gln Gln 1152 cag gac caa gtg gac cgc aac atc aag gag gct cgt gag aag ctg gag Gln Asp Gln Val Asp Arg Asn Ile Lys Glu Ala Arg Glu Lys Leu Glu

295

						cgc Arg										1200
_	_	_	_		-	caa Gln 325	-	-				_	_		_	1248
						aaa Lys	_	_		_				_		1296
_		_		_	_	gaa Glu	_		_			_		_	_	1344
_	_		-	_	_	gaa Glu			_					-		1392
_		_				atg Met		_	_	_	_			_	_	1440
						gcc Ala 405										1488
		-				cct Pro	_		_	_	_	_			_	1536
	_					act Thr	-	-			_	-	-		-	1584
_						ggt Gly					-			_	_	1632
						gcc Ala								taa *	taa	1680
gtto	gcagt	gt o	ctagt	ttct	c aa	aaacc	cctta	a aaa	agaaç	gac	cctt	tttç	gga c	ctago	cagaa	1740
ttct	acco	ctg g	gaaaa	agtgt	it aç	ggat	tcct	tcc	caata	ıgtt	agat	ctac	ccc t	gcct	gtact	1800
acto	tago	gga g	gtato	gatgg	ga gg	gcaga	agggo	c aag	ggag	iggg	tggt	atta	aa c	caagt	caatt	1860
ctga	aaaa	aaa a	aaaa	ì												1875

<210> 120

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gag ggc tgg ccc Glu Gly Trp Pro . 180		Gly Tyr Thr		-
gca gag gac acc Ala Glu Asp Thr 195				
ttc tga agctgcca Phe * 210	ca ggggaggagt c	tcttctcag tg	agggtctc cgggag	tccc 736
tcagcttcta catca	gcctg aatgacgag	g ctgtctcttt	ggatgatgcc tag	gcccaaa 796
ggagaggcca aaagg	gaaac caaggctgc	a cacctagaac	cccaattcag cct	cctgggc 856
accccagagg caagg	ctgtg cactcaggg	a gggagggtgg	gacacagagg tgc	atctagg 916
gtcccacctg taccc	ttgct ctttcctct	c ttagccctta	gaagtcacct act	tccttcc 976
agtgccatga tccca	cctgc gacctctag	t gcgagtgcag	agaaggtggg acc	agggcca 1036
gggttccaaa aagag	aataa gcctcctgg	g gggtctgacc	tagttagttc ttg	agtttgg 1096
ggtttccagt accate	ctgga tgccctgcc	t gttgagcccc	attctacatc ccc	accatta 1156
accaggcccc accca	caagg tagaaacaa	c ccctagagtc	aacgagaaag tca	ttttcag 1216
aaaatctaca agtct	cgttg agaccacca	c catacctcag	aaggtaggac tgt	ggcctag 1276
aagggaaagg aaagc	tgaga tgatgtctt	a ccgtagcagc	agatcttgga tgg	tccaggc 1336
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ccattgagga caacag	gc			1413

<210> 121

<211> 2554

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (164)..(2323)

<400> 121

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tgcgcacagc tccgcccacc cctccctgcc tccttttctt cctcagcggg tccgcggccc 120

gctactctcc gggaggggcg cttcccgacg ccaagacaaa agg atg cca cgg aga
Met Pro Arg Arg
1

						gtc Val										223
-		_			-	tct Ser	-	_		_		_	_	_		271
						ata Ile										319
	_			-	_	aaa Lys	_	_			_	_		_	-	367
-		-	-			aaa Lys 75										415
						atg Met										463
_	_			_	_	gag Glu			_			_		_	_	511
-	_		_	_		cct Pro		_	-		_		_		_	559
	_	-			_	tct Ser		_								607
_					_	ggc Gly 155			_	-	-					655
						agt Ser					_		_	_		703
			_			gaa Glu			_			_	_			751
_			-		-	cag Gln		_	-		-					799
	_				_	aga Arg	_				_	_				847
cag	tgt	ggg	aag	cca	cag	gaa	agt	act	ggg	agg	ggt	tct	gct	ttt	ctc	895

Gln	Cys 230	Gly	Lys	Pro	Gln	Glu 235	Ser	Thr	Gly	Arg	Gly 240	Ser	Ala	Phe	Leu	
	gct Ala	_	_		_		_					_				943
	gca Ala	_	_				_	-								991
	tgg Trp					_		_		-	-			_		1039
	aag Lys															1087
_	gct Ala 310	_		-									_			1135
	cct Pro	_				_										1183
_	gct Ala	_				-	-			-	-	_		-	-	1231
_	aaa Lys				_	-			_		_					1279
	aag Lys	_		_	_	_				_	_					1327
	ttg Leu 390															1375
	gtt Val	-				-										1423
_	gtt Val	-	-	_		_	_	-	-		_		_			1471
_	tct Ser	_	_	-			_	_				_		_		1519
	gaa Glu															1567

465

ato Ile	ttg Leu 470	ı Asr	gga Gly	gto Val	aga Arg	ata Ile 475	I1e	atg Met	gca : Ala	ı gat ı Asp	aag Lys 480	s Glu	gtt Val	ggt Gly	aac Asn	1615	5
aag Lys 485	: Glu	gat Asp	gct Ala	gag Glu	aag Lys 490	Glu	gta Val	gct Ala	att Ile	tct Ser 495	Thr	ttc Phe	tca Ser	tcc Ser	agt Ser 500	1663	3
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gta Val	ttg Leu	act Thr 535	cgg Arg	aga Arg	caa Gln	aaa Lys	gag Glu 540	gcc Ala	aag Lys	acc Thr	aag Lys	agt Ser 545	gac Asp	agt Ser	Gly aaa	1807	
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gaa Glu 645	aca Thr	gga Gly	gcc Ala	ttc Phe	agg Arg 650	gtg Val	cct Pro	tca Ser	cca Pro	ggg Gly 655	atg Met	gaa Glu	gag Glu	gca Ala	ggc 660	2143	
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tct Ser	ccc Pro	Val	aag Lys 680	tct Ser	ttt Phe	gtt Val	Ser	att Ile 685	tca Ser	gaa Glu	gcc Ala	aca Thr	gat Asp 690	tgc Cys	tta Leu	2239	

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acc aaa gct ggc aga gga aga agg aga aaa ttc tga attt ctagggtcca Thr Lys Ala Gly Arg Gly Arg Arg Arg Lys Phe * 710 715 720	2337
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694

agt ccc atc aag aga aaa cca cag act ctg ggc tca ctg aag tct tcc Ser Pro Ile Lys Arg Lys Pro Gln Thr Leu Gly Ser Leu Lys Ser Ser 20 25 30

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		_	-	-	-	gag Glu	_	_	_	-						982
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						gcc Ala										1078
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_			-			ctg Leu	-			_			_	_		1222
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						tgt Cys										1318
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agt	ttc	ttg	gaa	cag	tct	gag	cac	aag	act	tca	gat	gca	gac	atc	aag	1414

tct tca gaa aca gga gcc ttc agg gtg cct tca cca ggg atg gaa gag Ser Ser Glu Thr Gly Ala Phe Arg Val Pro Ser Pro Gly Met Glu Glu 275
Ala Gly Cys Ser Arg Glu Met Gln Ser Ser Phe Thr Arg Arg Asp Leu 290 295 300 aat gaa tct ccc gtc aag tct ttt gtt tcc att tca gaa gcc aca gat Asn Glu Ser Pro Val Lys Ser Phe Val Ser Ile Ser Glu Ala Thr Asp 305 310 315 320 tgc tta gtg gac ttt aaa aag caa gtt act gtc cag cca ggt agt cgg Cys Leu Val Asp Phe Lys Lys Gln Val Thr Val Gln Pro Gly Ser Arg
Asn Glu Ser Pro Val Lys Ser Phe Val Ser Ile Ser Glu Ala Thr Asp 305 310 315 320 tgc tta gtg gac ttt aaa aag caa gtt act gtc cag cca ggt agt cgg 1606 Cys Leu Val Asp Phe Lys Lys Gln Val Thr Val Gln Pro Gly Ser Arg
Cys Leu Val Asp Phe Lys Lys Gln Val Thr Val Gln Pro Gly Ser Arg
aca cgg acc aaa gct ggc aga gga aga agg aga aaa ttc tga atttcta 1655 Thr Arg Thr Lys Ala Gly Arg Gly Arg Arg Lys Phe * 340 345 350
gggtccaaaa gttgacaaaa ccattagtag gaggggtggg ccatgttcat taagccatag 1715
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tgtgtgtttg tgtgtgtgt tgcactcaag acctctaaca gcctcgaagc ctggggtggc 180

atg cat cat cag atg aca agg aca Met His His Gln Met Thr Arg Thr 231

atcccggcct tgccattagc atgcctc

	ctc Leu 10															279
	aat Asn															327
	tct Ser															375
	aca Thr															423
	act Thr															471
	ctc Leu 90															519
	ccg Pro															567
	caa Gln															615
	ttt Phe														tga *	663
agg	atgco	cag t	tacto	gtggt	g to	gtgag	rtctc	ago	cagco	gcc	caca	cgct	cc t	aact	ctgct	723
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cta	gcato	ıtg d	ctgca	ıttga	ac to	ctatt	aato	aca	tttc	aaa	ttca	ccct	ac a	ttcc	tctcc	963
tct	tcact	ag d	cctct	ctga	a gg	gtgtc	ctgg	cca	igaca	tgg	agaa	gcac	tg ç	rtgtc	tgcag	1023
cac	ccctc	ag t	tcct	gtgc	c to	cagco	caca	ggc	cact	gtg	ataa	tggt	ct g	rttta	gcact	1083
tct	gtatt	ta t	tgta	agaa	ıt ga	ttat	aatg	aag	gatac	aca	ctgt	aact	ac a	agaa	attat	1143
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tat	ttqca	aa c	acact	ctat	a σc	taca	tatt	ato	raaaa	tag	ataa	ctaa	tc a	gaat	aataa	1263

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1 5

Thr	Glu	Val	Val 10		Leu	Ala	Cys	Gly 15		Phe	Asn	Pro	Ile 20		Asn	
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												Val			gcc Ala	256
															gca Ala 70	304
															gaa Glu	352
	ctt Leu															400
	gag Glu															448
act Thr	cta Leu 120	gaa Glu	agg Arg	cct Pro	gga Gly	agg Arg 125	aag Lys	agg Arg	aag Lys	tgg Trp	act Thr 130	gaa Glu	aca Thr	caa Gln	gat Asp	496
tct Ser 135	agt Ser	caa Gln	aag Lys	aaa Lys	tcc Ser 140	cta Leu	gag Glu	cca Pro	aaa Lys	aca Thr 145	aaa Lys	gct Ala	gtg Val	cca Pro	aag Lys 150	544
	aag Lys															592
aat Asn	ttg Leu	tgg Trp	aag Lys 170	agt Ser	gaa Glu	gac Asp	atc Ile	acc Thr 175	caa Gln	atc Ile	gtg Val	gcc Ala	aac Asn 180	tat Tyr	Gly	640
ctc Leu	ata Ile	tgt Cys 185	gtt Val	act Thr	cġg Arg	gct Ala	gga Gly 190	aat Asn	gat Asp	gct Ala	cag Gln	aag Lys 195	ttt Phe	atc Ile	tat Tyr	688
gaa Glu	tcg Ser 200	gat Asp	gtg Val	ctg Leu	tgg Trp	aaa Lys 205	cac His	cgg Arg	agc Ser	aac Asn	att Ile 210	cac His	gtg Val	gtg Val	aat Asn	736
gaa Glu 215	tgg Trp	atc Ile	gct Ala	aat Asn	gac Asp 220	atc Ile	tca Ser	tcc Ser	aca Thr	aaa Lys 225	atc Ile	cgg Arg	aga Arg	gcc Ala	ctc Leu 230	784
aga Arg	agg Arg	ggc Gly	cag Gln	agc Ser	att Ile	cgc Arg	tac Tyr	ttg Leu	gta Val	cca Pro	gat Asp	ctt Leu	gtc Val	caa Gln	gaa Glu	832

				235					240					245		
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aca Thr		gaa	ttct	aca (gcat	gata	tt t	caga	cttc	c ca	tttg	ggga	tct	gaaa	caa	984
tct	gggag	gtt a	aataa	actg	aa a	aaaga	aagt	t gt	gatc	tgtt	gcc.	taaa	cta .	aagc	ttaaaa	1044
gtt																1047
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											gtg Val					147
											aaa Lys					195
								_			aac Asn					243
											cgg Arg					291
											gag Glu					339

90	95	100	
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gtg aac gcc tga Val Asn Ala *	acg tcacatgggt	tcataaaaga gagctggccg aagagaacaa	442
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		gct gct gag gag ttt gtc aat att Ala Ala Glu Glu Phe Val Asn Ile 20	219
Tyr Tyr Glu Thr	atg gat aaa aga Met Asp Lys Arg 30	aga cgg gca cta acc agg ctg tat Arg Arg Ala Leu Thr Arg Leu Tyr 35 40	267
		aat gga aat gct gtt tca ggg ctg Asn Gly Asn Ala Val Ser Gly Leu 50 55	315
		aca ttg cct tct agt gag ttc cag Thr Leu Pro Ser Ser Glu Phe Gln 65 70	363
		gtt cat gag caa gca act cag tcc Val His Glu Gln Ala Thr Gln Ser 85	411
		agt gga act gtg aag ttt gat gga Ser Gly Thr Val Lys Phe Asp Gly	459

aac aaa caa cat ttc ttc aac cag aac ttc ctg ctg act gct cag tc Asn Lys Gln His Phe Phe Asn Gln Asn Phe Leu Leu Thr Ala Gln Se 105 110 115	r
act ccc aac aat act gtg tgg aag att gca agt gat tgc ttc cgt tt Thr Pro Asn Asn Thr Val Trp Lys Ile Ala Ser Asp Cys Phe Arg Phe 125 130 135	
caa gat tgg tct agt agt taa ag gggcaaaagt ccattctcat ttggtccat Gln Asp Trp Ser Ser Ser * 140	t 608
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Met Asn Phe
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ata aca gtg att caa ata ttt cat tca gat tta cct atg cct aat gaa

Ile Thr Val Ile Gln Ile Phe His Ser Asp Leu Pro Met Pro Asn Glu

20 25 30 35

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					tat Tyr										429
	-				aaa Lys	-	-				-	-	-		477
-					tcc Ser	-	_		-	-	-				525
		_	_		aaa Lys 105			_		-			_	_	573
		-			tct Ser		_	-	-	-		_			621
	_	_			gtt Val	-	_				_				669
	-				gct Ala	_	_	_	_				_	_	717
					tat Tyr							-	_	-	765
	-	-		-	aaa Lys 185	_							_		813
					gat Asp										861
_	_	_		_	gag Glu		-			_	_		_		909
					aat Asn										957
_					cgt Arg		-		-	-			_		1005
					ata Ile 265				-		-				1053

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						agc Ser										1149
						gcc Ala					-				-	1197
						tta Leu 330										1245
						tca Ser										1293
						atg Met										1341
						ccg Pro										1389
		_	_			aga Arg			-		_				_	1437
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						agt Ser										1581
	_	_				gat Asp	_		_	_	_			_		1629
						aat Asn										1677
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Ile Phe Glu His Leu Glu Gly Leu Ser Gln Val Phe Ser Asp Cys Phe 500 505 510 cca cca gaa caa gac ttg cgt tca gga aat ttg tgg ata att cac cct 1821 Pro Pro Glu Gln Asp Leu Arg Ser Gly Asn Leu Trp Ile Ile His Pro 520 530 ttt atg aat cac caa aat aat ctc acc gac ttc gaa gaa gaa aag 1869 Phe Met Asn His Gln Asn Asn Leu Thr Asp Phe Glu Glu Lys 535 540 cta aca gag cta tct tca gat tta gga tta caa gca cta ttt aaa tca 1917 Leu Thr Glu Leu Ser Ser Asp Leu Gly Leu Gln Ala Leu Phe Lys Ser 555 gtg tct gta act cag ttt tgg ata aat gca aag aca agt tac cca gaa 1965 Val Ser Val Thr Gln Phe Trp Ile Asn Ala Lys Thr Ser Tyr Pro Glu 570 ctc cat gaa agg gca atg aaa ttt tta tta ccc ttt tca act gtt tat 2013 Leu His Glu Arg Ala Met Lys Phe Leu Leu Pro Phe Ser Thr Val Tyr 580 585 590 tta tgt gat gct ttt tca gct ttg act gag tca aaa caa aaa aat 2061 Leu Cys Asp Ala Ala Phe Ser Ala Leu Thr Glu Ser Lys Gln Lys Asn 600 605 ctg ttg ggt tct ggc cct gcc cta aga ctt gca gtc aca tct tta att 2109 Leu Leu Gly Ser Gly Pro Ala Leu Arg Leu Ala Val Thr Ser Leu Ile 615 620 cca agg ata gaa aaa tta gtg aag gag aaa gag tag caat atgcacattg 2159 Pro Arg Ile Glu Lys Leu Val Lys Glu Lys Glu * 630 cttaacagtg aagtcaataa tcctgtgtta agttttgtat aagtatccta aaagataatt 2219 tcctaatgtg gatttgtgtt ttcagtgatt aaatgtttta ataatttttc cctttttgtt 2279 gaggaattta ataattatga ttgttataaa taattatgta taattataat ctagggtaga 2339 aaatttagtt atttcattaa atttggacta gtgacaaaga ctgcaggtaa tgagaagccc 2399 agtttataat gtaacagcac aacctggatg ttgaaacagc ttggccttta gaagcaagtg 2459 gaacatttca gtcttctagc caaccagcta cttacccctg caaggttgtg agtaggtgga

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		_	_	_	_	~	_	ccg Pro	~	-		_		-	•	306
								gcg Ala								354
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								gaa Glu								690

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cga gat gtt ttg gag gcc ctt gct ttt ctt cat cat gag ggc tat gtc Arg Asp Val Leu Glu Ala Leu Ala Phe Leu His His Glu Gly Tyr Val 140 145 150 155	543
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-		_		-	att Ile		-				-	-		-		879
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-	-				agc Ser 305				_				_	_	_	1023
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Met Met Thr His Leu His Val Lys Ser Thr Glu Pro

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351

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_	_	_	_	_								_		aga Arg	-	293
		_	_		_		-	_				-		ggt Gly		341
				_				_		_				atg Met		389
	_	_	_		gtg Val 125	_		_	taa *	t aa	atgcg	gagco	c aga	attaa	attt	440
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aca act gac aaa tgc aac gcc cac ctc atg act cat gac gcc ctc ccc Thr Thr Asp Lys Cys Asn Ala His Leu Met Thr His Asp Ala Leu Pro 65 70 75	421
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cga cga gtc cag tgt cac cag gac cag acc gcc tgc ttc cag ggc aat Arg Arg Val Gln Cys His Gln Asp Gln Thr Ala Cys Phe Gln Gly Asn 110 115 120	565
ggc aga atg aca gtt ggc aat ttc tca gtc cct gtg tac atc aga acc Gly Arg Met Thr Val Gly Asn Phe Ser Val Pro Val Tyr Ile Arg Thr 125 130 135 140	613

											acc Thr					661
											tac Tyr					709
		_		_				_	_		gcc Ala					757
											gtc Val 200					805
	ctc Leu				acc	geee	etc (cagga	atgct	a ad	ggaca	gggd	c tca	acaca	acct	860
catt	ctte	gat g	gctto	cagco	cc ct	tatca	acata	a gct	cact	gga	aaat	gate	gtt a	aaagt	caagaa	920
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atg	gtc	aac	gtc	ttg	aaa	gga	gtg	ctt	ata	gaa	ctga tgt Cys	gat	cct	gcc		119 167
											gcc Ala					215
											ttt Phe					263
											tta Leu					311

gct ttt tcc ctt acc cag aaa tga aaatactcaa tatggaccat ttaggaatta Ala Phe Ser Leu Thr Gln Lys * 65 70	365
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cgc gag aaa cag aag ctc ttc cag gtg ggg ggg gcg ggg ggg gtg ggg Arg Glu Lys Gln Lys Leu Phe Gln Val Gly Gly Ala Gly Gly Val Gly 30 35 40	148
atc cga cgc gcc agc cgg gag cgc gcc gag ccg ggg cag gcg ggg cgc Ile Arg Arg Ala Ser Arg Glu Arg Ala Glu Pro Gly Gln Ala Gly Arg 45 50 55	196
gct cta agg agc agc cag cac ccc ttt ctc atc aga cac ccc cac atc Ala Leu Arg Ser Ser Gln His Pro Phe Leu Ile Arg His Pro His Ile 60 65 70	244
cag gag gac aat gac atc ccg ttg tac ctg aag ggc ggc atc gtt gac Gln Glu Asp Asn Asp Ile Pro Leu Tyr Leu Lys Gly Gly Ile Val Asp 75 80 85 90	292
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tac agc ttg tac tcc ctt ggc tgg gcc tcc ttc ccc agg aat taa gac Tyr Ser Leu Tyr Ser Leu Gly Trp Ala Ser Phe Pro Arg Asn * 110 115 120	388
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aaaaaaaaa a 459

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gtgaaactgg				g ttc cct tt t Phe Pro Ph		229
	t ctg tca gtt l Leu Ser Val 15		g Lys Ile			277
	g gtg tta act ı Val Leu Thr)	-				325
	a gcc tat ctc a Ala Tyr Leu					373
	g acc aaa agt y Thr Lys Ser 65	Thr Glu Ph				421
	a cat tgc ctt D His Cys Leu 80	_				469
	c tgc gcg tcg 7 Cys Ala Ser 95		s Glu Met			517
	c tta gct atc a Leu Ala Ile)					565
~	c cag gca atg c Gln Ala Met	• • •	~ ~			613

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gaagcgcgaa gctgggattt tttactgtct cctgaagaat ttaacacaaa c atg gat Met Asp 1	177
atc aga cca aat cat aca att tat atc aac aat atg aat gac aaa att Ile Arg Pro Asn His Thr Ile Tyr Ile Asn Asn Met Asn Asp Lys Ile 5 10 15	225
aaa aag gaa gaa ttg aag aga tcc cta tat gcc ctg ttt tct cag ttt Lys Lys Glu Glu Leu Lys Arg Ser Leu Tyr Ala Leu Phe Ser Gln Phe 20 25 30	273
ggt cat gtg gtg gac att gtg gct tta aag acc atg aag atg agg ggg Gly His Val Val Asp Ile Val Ala Leu Lys Thr Met Lys Met Arg Gly 35 40 45 50	321
cag gcc ttt gtc ata ttt aag gaa ctg ggc tca tcc aca aat gcc ttg Gln Ala Phe Val Ile Phe Lys Glu Leu Gly Ser Ser Thr Asn Ala Leu 55 60 65	369
aga cag cta caa gga ttt cca ttt tat ggt aaa cca atg cga ata cag Arg Gln Leu Gln Gly Phe Pro Phe Tyr Gly Lys Pro Met Arg Ile Gln 70 75 80	417
tat gca aaa aca gat tcg gat ata ata tca aaa atg cgt gga act ttt Tyr Ala Lys Thr Asp Ser Asp Ile Ile Ser Lys Met Arg Gly Thr Phe 85 90 95	465
gct gac aaa gaa aag aaa aaa gaa aag aaa aaa	513

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ccg tcc cat gct atg aag atc acc tat gcc aag aaa taa catttgggat Pro Ser His Ala Met Lys Ile Thr Tyr Ala Lys Lys * 165 170 175	706
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teg cag gaa gac tet aat ttg tee gag gag ttg tet cae tee gee ttt Ser Gln Glu Asp Ser Asn Leu Ser Glu Glu Leu Ser His Ser Ala Phe 15 20 25	218
gga cag gcc ttc tcc aag att tta cac tgt ctt gcc cgc ccg gag gca Gly Gln Ala Phe Ser Lys Ile Leu His Cys Leu Ala Arg Pro Glu Ala 30 35 40	266
cga cga ggc aat gta aaa gat gca gtt ctt aaa gac ctc ggt gat cta Arg Arg Gly Asn Val Lys Asp Ala Val Leu Lys Asp Leu Gly Asp Leu 45 50 55	314

		Ala			ttt Phe											362
					gag Glu 80											410
					tcc Ser											458
	-	-	-		aaa Lys	-	_		-			_				506
_				_	gag Glu		-	-			_	-			-	554
	_	_		_	cat His		-	_			_				_	602
			-	_	gag Glu 160						_	_			-	650
					ctc Leu			_			_		_	_		698
					cta Leu										-	746
					ggg Gly									-		794
	-				gcc Ala				_					_		842
_	_		~ ~		tgg Trp 240	_	_	_		_	-		_			890
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					cat His											986

-		_			-	gcc Ala	_	_				_				1034
	_					cac His 305				_	_			-	_	1082
_	_	-				atc Ile	_				_					1130
_		_	_			acc Thr		_	_		_	_		_		1178
_			-			gag Glu		_				_				1226
_	_		-	_		ttc Phe				-					_	1274
			-		-	gag Glu 385	_	_					_		_	1322
						gaa Glu										1370
			_			act Thr			_	_		_	_			1418
						ttg Leu										1466
						tct Ser	_	_	_	_	-		_		-	1514
						ctg Leu 465										1562
		_	_			ccc Pro		_	_	_	-	_				1610
						cag Gln										1658
gga	act	taa	gact	tgt	atta	cttt	cc c	aaga	ıggaa	a gg	attt	tctt	ccc	catco	caa	1714

Gly Thr *

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			gac acc acc atg age Asp Thr Thr Met Se: 20	
			cca gag ccc cgg cgc Pro Glu Pro Arg Arg 35	
	Ala Pro Ser Se		cca gtg gcc ctg acc Pro Val Ala Leu Th: 50	
			ctg gca gcc ctg ggg Leu Ala Ala Leu Glg 65	
_	_	_	act ggt caa gac acc Thr Gly Gln Asp Th:	r -
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_	=		agt ctg cag cat gtg Ser Leu Gln His Va 115	

gct gaa aaa ctc tgt cgt gag ctg tat aac aaa gct gga gca cac agg Ala Glu Lys Leu Cys Arg Glu Leu Tyr Asn Lys Ala Gly Ala His Arg 120 125 130	498
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cag ttc tat aaa gac agc aaa agt tgg gag gac tgt aaa tat ttc tgc Gln Phe Tyr Lys Asp Ser Lys Ser Trp Glu Asp Cys Lys Tyr Phe Cys 150 165	594
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gga acc cct ttc act tct gaa ctg ttc cat att ata ata gat gtc acc Gly Thr Pro Phe Thr Ser Glu Leu Phe His Ile Ile Ile Asp Val Thr 215 220 225	786
agc cca aga agc aga gac tgt gtg gcc atc ctt aat ggg atg atc ttc Ser Pro Arg Ser Arg Asp Cys Val Ala Ile Leu Asn Gly Met Ile Phe 230 245	834
tca aag gac tgc aaa gaa ttg aag cgt tgt gtc tgt gag aga agg gca Ser Lys Asp Cys Lys Glu Leu Lys Arg Cys Val Cys Glu Arg Arg Ala 250 255 260	882
gga atg gtg aag cca gag agc ctc cat gtc ccc cct gaa aca tta ggc Gly Met Val Lys Pro Glu Ser Leu His Val Pro Pro Glu Thr Leu Gly 265 270 275	930
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		cac His 40														258
~	_	act Thr	~	_	_		_	_			_	-	_	_		306
	_	ttt Phe		_			_							-		354
		caa Gln	_	_	_	_				_				_		402
		caa Gln														450
-	-	aaa Lys 120		-	-		-				_					498
_		atg Met			_		-				_			_		546
		atg Met		_	_	_	_	-			-	-		_		594
-		tgg Trp					_		_		_				_	642
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		ctg Leu 200														738
		tac Tyr														786
		agt Ser														834
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			gtg Val													158
	-		gaa Glu	_				-			-	_		_		206
			tcc Ser										_		_	254
			gcg Ala 65													302
			gtg Val													350
			aag Lys													398
			gtg Val													446
			tcc Ser													494
			ttt Phe 145													542

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gatttteetg gaaaattata ggtgeeeage taagaeetga atgeeateae eeteeeagg 300

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356

atq

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					Gly											404
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			_	-	ttt Phe									_	_	500
			-		aaa Lys 55			-		-		_	_			548
					aaa Lys											596
	_				cac His		_	-			-		_		-	644
			_		cag Gln											692
_					gat Asp			-	-		-		-			740
					gat Asp 135											788
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					ctg Leu											980
					att Ile											1028

210					215					220					225	
													ctg Leu			1076
	_		_		-	_				_			aga Arg 255	_	_	1124
													agg Arg	-		1172
													tca Ser			1220
					-			_			-		cac His			1268
		-							_	_			ctc Leu	_	_	1316
													atc Ile 335			1364
ccg Pro	tga *	aagt	ttat	tt t	tgto	tgaa	aa go	ettto	ataa	a gta	attta	aat	caac	acag	yta	1420
atca	acta	itt t	aatt	gcto	gc aa	ıtcgg	gtcaa	a aat	ttac	caaa	agco	cacac	cac a	aatt	tctct	1480
cctt	ctac	cac g	rtago	ctcca	at ac	cacto	gecec	ttg	ıccaa	aca	ccct	tacg	ggg a	acca	atcag	1540
catg	racat	tc c	tggg	gcagt	t aa	ıtgtg	gagaa	gcg	aggg	gcag	ggca	accgt	cc n	agto	ggactt	1600
tato	cttc	ag g	gagg	ggcg	yt at	ccto	ctctc	tta	cact	ctg	tgtg	ıtggt	ta a	attt	ctaaa	1660
gaac	acca	itt t	aato	cata	g ct	atat	cag									1689

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<211> 480

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<213> Homo sapiens

<220>

<221> CDS

<222> (104)..(298)

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gta gct ttt cag tgt ttc ttc tgc ttt tgg ttt gtt gag ctt ttt gga Val Ala Phe Gln Cys Phe Phe Cys Phe Trp Phe Val Glu Leu Phe Gly 5 10 15 20	163
ttt gtg ggt tta cag tta tta tca aat ttg gaa aaa ttt cag ccc tta Phe Val Gly Leu Gln Leu Leu Ser Asn Leu Glu Lys Phe Gln Pro Leu 25 30 35	211
tgt ctt caa ata ttt ttt ctg tct ccc tgc ccc atc cgt agt ctt tat Cys Leu Gln Ile Phe Phe Leu Ser Pro Cys Pro Ile Arg Ser Leu Tyr 40 45 50	259
ata ttt gat cat cta aag ttg tct cac agc tca cag tga cactgcttgt Ile Phe Asp His Leu Lys Leu Ser His Ser Ser Gln * 55 60 65	308
ttttccagtc ttttttccc tctaggtgtt tcattttgaa caattgctat tgctatgtct	368
tcaagatcct taatcttttc ttctgtagtg ccacatctta cccagtgaac ttttcacctc	428
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ggtaccaggc actgggggtg gggagggaag acagggt atg ggg agg agg gat ggt Met Gly Arg Arg Asp Gly 1 5	175
gat gaa aga agc tgt tct gga tta ggg act cca aag gca gct gac agc Asp Glu Arg Ser Cys Ser Gly Leu Gly Thr Pro Lys Ala Ala Asp Ser 10 15 20	223
atc tgg ctt tca gtt cct cag tca cca cta ctt tgt acc aaa ttc act Ile Trp Leu Ser Val Pro Gln Ser Pro Leu Leu Cys Thr Lys Phe Thr	271

gtt ttg gct ctg aaa tct aat ttt gag ttt agc aag gat gtc tgc att Val Leu Ala Leu Lys Ser Asn Phe Glu Phe Ser Lys Asp Val Cys Ile 40 45 50	319
gct cat gca aat gaa cta agc gtt cat tgg aat gac acc atc acc acc Ala His Ala Asn Glu Leu Ser Val His Trp Asn Asp Thr Ile Thr Thr 55 60 65 70	367
caa atg aaa aga act ggc tgg aat att cat cag cct act aat gtc atc Gln Met Lys Arg Thr Gly Trp Asn Ile His Gln Pro Thr Asn Val Ile 75 80 85	415
tcc caa ccc act ctc caa act cca tcc caa aaa a	463
att gcc cac tgt tgg caa aga aag aat gtc act aat tta ttt aca ggg Ile Ala His Cys Trp Gln Arg Lys Asn Val Thr Asn Leu Phe Thr Gly 105 110 115	511
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atggacctgc atcttccctg aagcatctcc agggctgaaa aatcactgac c atg gca Met Ala 1	177
cca tgg tct cat cca tct gca cag ctg cag cca gtg gga gga gac gcc Pro Trp Ser His Pro Ser Ala Gln Leu Gln Pro Val Gly Gly Asp Ala 5 10 15	225
gtg agc cct gcc ctc atg gtt ctg ctc tgc ctc ggg ctg agt ctg ggc Val Ser Pro Ala Leu Met Val Leu Cys Leu Gly Leu Ser Leu Gly 20 25 30	273
ccc agg acc cac gtg cag gca ggg aac ctc tcc aaa gcc acc ctc tgg Pro Arg Thr His Val Gln Ala Gly Asn Leu Ser Lys Ala Thr Leu Trp 35 40 45 50	321

_					gtg Val		_								369
					gag Glu										417
_		_			gac Asp		-			-		-		-	465
					cca Pro								-		513
_	-				agc Ser 120		_					_	~		561
_		_			aca Thr									_	609
					gtg Val								_	-	657
					ttc Phe							_		_	705
					acc Thr										753
					cct Pro 200										801
					ggc Gly										849
					ctg Leu										897
		_			aac Asn	_		_			_				945
_	-		-	_	gag Glu				_	_	 _	_		_	993

	Leu														cag Gln 290	1041
		ccc Pro								a c	agaa	gaga	g aa	caat	gcac	1092
cat	tgaa	tgc	tgga	gcct	tg g	aagc	gaat	c tga	atgg	tcct	agg	aggt	tcg	ggaa	gaccat	1152
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cacegorgica godococtacg caggoracgo cactg atg cac acc aaa coc aat Met His Thr Lys Pro Asn									173							
		ggc Gly														221
		cca Pro 25						Gln								269
		cta Leu			-			-	_		_		-		-	317
		ggt Gly														365
		aga Arg				_						-				413
		caa Gln				_			_		-	-	_			461

aac aca gca cca aca gct tcc aag ata gta aca gac tcc aat tcc agg Asn Thr Ala Pro Thr Ala Ser Lys Ile Val Thr Asp Ser Asn Ser Arg 105 110 115	509
gtt tca gaa ccg cat cgc agc atc ttt cct gaa atg cac tca gac tca Val Ser Glu Pro His Arg Ser Ile Phe Pro Glu Met His Ser Asp Ser 120 125 130	557
gcc agc aaa gac gtg cct ggc cgc atc ctg ctg gat ata gac aat gat Ala Ser Lys Asp Val Pro Gly Arg Ile Leu Leu Asp Ile Asp Asn Asp 135 140 145 150	605
acc gag agc act gcc ctg tga ag aaagcccttt cccagccctc caccacttcc Thr Glu Ser Thr Ala Leu * 155	658
accctggcga gtggagcagg ggcaggcgaa cctctttctt tgcagaccga acagtgaaaa	718
gctttcagtg gaggacaaag gagggcctca ctgtgcggga cctggccttc tgcacggccc	778
aaggagaacc tggaggccac cactaaagct gaatgacctg tgtcttgaag aagttggctt	838
tctttacatg ggaaggaaat catgccaaaa aaatccaaaa caaagaagta cctggagtgg	898
agagagtatt cctgctgaaa cgcgcatagg aagcttttgt ccctgctgtt aatgcgggca	958
gcacctacag caacttggaa tgagtaagaa gcagtgcgtt aactatctat ttaataaaat	1018
gcgctcatta tgcaagtcgc ctactctctg ctacctggac gttcattctt atgtattagg	1078
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tctccccagt cccctcagaa ccatgcccat ggatggtgac tgctggctct gtcacctcat	1198
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gt	1260

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<211> 1929

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<213> Homo sapiens

<220>

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caagatgatg catggctgga caaaatctac agacgctatg cctggataaa acgccagctt 180

gtggactatg aggagaaata cggccgc atg ttt cca cgt gag tgg tgc atg Met Phe Pro Arg Glu Trp Cys Met 1 5									
gct gag agg att gcg Ala Glu Arg Ile Ala 10									
gcc aag att atg cgt Ala Lys Ile Met Arç 25									
ctt ttt gct att caa Leu Phe Ala Ile Glr 45	Arg Thr Thr			_					
cgc ttc tcc ggc tgc Arg Phe Ser Gly Cys 60	_		-						
tct cca ccc cca tct Ser Pro Pro Pro Ser 75		Phe Leu Glu							
gag atg gag gaa ctg Glu Met Glu Glu Lev 90			~	-					
aag cct aaa gcc cca Lys Pro Lys Ala Pro 105	_		-						
ttt gag cct cat ctc Phe Glu Pro His Lev 125	ı Tyr Val Tyr		Gln Asp Lys						
gga gag ctg ata gat Gly Glu Leu Ile Asr 140									
cct aag ccc aac act Pro Lys Pro Asn Thr 155									
gac ctc ttt gtc tac Asp Leu Phe Val Tyr 170			-	•					
agt act ggg gag ccc Ser Thr Gly Glu Pro 185	-	-	_	-					
ctc cga gaa tac gcc Leu Arg Glu Tyr Ala 205	Trp Lys Ile		Asn Leu Pro						
aca acc agc agt gga	ı gga ctg act	atc agc agc	ctc ctc aag	gaa aag 903					

Thr	Thr	Ser	Ser 220	Gly	Gly	Leu	Thr	Ile 225	Ser	Ser	Leu	Leu	Lys 230	Glu	Lys	
gag Glu	ggc Gly	tca Ser 235	gaa Glu	gta Val	gcc Ala	aag Lys	ttc Phe 240	act Thr	ctg Leu	gag Glu	gag Glu	ctc Leu 245	tgc Cys	ctc Leu	atc Ile	951
tgt Cys	aac Asn 250	atc Ile	ctg Leu	agc Ser	acg Thr	gca Ala 255	gag Glu	tac Tyr	tgt Cys	ctg Leu	gcc Ala 260	acc Thr	acc Thr	cag Gln	cag Gln	999
cta Leu 265	gaa Glu	gaa Glu	aaa Lys	ctc Leu	aaa Lys 270	gaa Glu	aaa Lys	gtg Val	gat Asp	gta Val 275	agt Ser	ctg Leu	att Ile	gaa Glu	cga Arg 280	1047
atc Ile	aat Asn	ctg Leu	act Thr	gga Gly 285	gag Glu	atg Met	gac Asp	acg Thr	ttc Phe 290	agc Ser	acc Thr	gtc Val	atc Ile	tcc Ser 295	agc Ser	1095
agt Ser	att Ile	cag Gln	ctg Leu 300	ctg Leu	gtt Val	cag Gln	gat Asp	ctg Leu 305	gat Asp	gct Ala	gcc Ala	tgt Cys	gat Asp 310	cct Pro	gcc Ala	1143
ctg Leu	act Thr	gcc Ala 315	atg Met	agc Ser	aag Lys	atg Met	cag Gln 320	tgg Trp	cag Gln	aac Asn	gtg Val	gag Glu 325	cac His	gtt Val	ggt Gly	1191
gac Asp	cag Gln 330	agc Ser	ccc Pro	tac Tyr	gtc Val	acc Thr 335	tct Ser	gtc Val	att Ile	ctg Leu	cac His 340	atc Ile	aag Lys	cag Gln	aac Asn	1239
gtc Val 345	ccc Pro	atc Ile	atc Ile	cgt Arg	gac Asp 350	aac Asn	ctg Leu	gct Ala	tcc Ser	aca Thr 355	cgc Arg	aag Lys	tac Tyr	ttc Phe	act Thr 360	1287
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cac His	ctc Leu	ttc Phe	aag Lys 380	tgc Cys	aag Lys	cca Pro	att Ile	agc Ser 385	atg Met	gtg Val	gga Gly	gca Ala	gaa Glu 390	cag Gln	gtg Val	1383
	tgg Trp			tat	cag	gcat	ttg	cctg	gcag	ct t	ttgt	tgta	g at	caag	caca	1438
tat	tctt	cta	gtcc	agat	ct a	cttg	gcag	g aa	taaa	attg	atg	atgt	ccc	ctgt	ttgggg	1498
aca	gtat	aat	gact	cacc	cg g	aagg	tttc	t ta	attc	gttc	ttc	catt	tat	tttt	aaaaat	1558
ttt	gttt	gaa	cgcc	tact	aa g	ttct	gggt	g ca	gggt	ataa	cac	agca	agc	acca	tggaaa	1618
ggt	ccct	gct	ccta	gtgc	tc a	cact	ccaa	t aa	gaag	aagt	ggc	tggg	ccg	ggca	cagcgg	1678
ctc	acgc	tgt	aacc	ccag	ca t	ttcg	ggag	g cc	tggg	cagg	cag	atca	cct	aaaa	taagga	1738

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Met Ala Leu Ala Ser Leu Arg Asn Leu Tyr Thr Pro Asn

1 5 10

ata aag gtc agc cga ctg ctg att ttg gga ggt gcc aat att aat tac 156

Ile Lys Val Ser Arg Leu Leu Ile Leu Gly Gly Ala Asn Ile Asn Tyr

15 20 25

cgg aca gag gtt tta aat aat gct cca att cta tgt gtt cag tcc cat
Arg Thr Glu Val Leu Asn Asn Ala Pro Ile Leu Cys Val Gln Ser His
30 45

ctt ggt tac aca gaa atg gta gcc ctg ctg ctg gag ttc ggg gcc aac
Leu Gly Tyr Thr Glu Met Val Ala Leu Leu Glu Phe Gly Ala Asn
50 55 60

gtg gat gcc tct tct gaa agt ggc ctg act ccc ctg gga tat gct gca
Val Asp Ala Ser Ser Glu Ser Gly Leu Thr Pro Leu Gly Tyr Ala Ala
65 70 75

gca gca ggg tac ctg agc att gtg gtg ctg ctg tgc aag aaa cgg gcc 348
Ala Ala Gly Tyr Leu Ser Ile Val Val Leu Leu Cys Lys Lys Arg Ala
80 85 90

aag gtg gat cat ttg gat aag aac ggg cag tgt gct ttg gtt cat gct
Lys Val Asp His Leu Asp Lys Asn Gly Gln Cys Ala Leu Val His Ala
95 100 105

gca ctc cga ggt cat ctg gag gtt gtc aag ttt ttg att cag tgt gac
Ala Leu Arg Gly His Leu Glu Val Val Lys Phe Leu Ile Gln Cys Asp
110 125

tgg acg atg gcc ggc cag cag caa gga gta ttt aag aag agc cat gcc 492
Trp Thr Met Ala Gly Gln Gln Gly Val Phe Lys Lys Ser His Ala

130	135	140
atc caa cag gcc ctc att gct gca gcc Ile Gln Gln Ala Leu Ile Ala Ala Ala 145 150		
aga agt agg caa tag gattgttttt tcaag Arg Ser Arg Gln * 160	getetg tattgaagga eed	aggaaac 595
caggagaaaa gattgcacga agacaaaatt gcc	caaccaaa ttaatgtgaa t	tcgtgatcg 655
ctgctctgaa taataaggag attaaactcc atg	gaagcact ttactcaaat ç	gccaaagtcc 715
ctcaaattat aggtatagaa aggtgcgagt tgg	gaaaggac cgtggaaatg a	atataattat 775
tctccatgtt ttcctccctg tttaacagac agt	ggcacca aggctcaaag a	agatgaatta 835
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acaaggctgt tgtaagggat gcttggtaaa ctg	yttaaaca ttatacagtt t	atttattaa 1075
tgataataac aataatagtg gcaaatgtag gga	aattggta gtgtgctagg a	aaatgtttaa 1135
caaccaactg tgaagagggg tgtggggtgg aac	aggggtg tgtgtttgtg t	gtgcatacg 1195
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atc act tcc tac gag aag ttt cta acc Ile Thr Ser Tyr Glu Lys Phe Leu Thr 10 15		
ctg gga cct cct cgc ggg gtg ggc acc Leu Gly Pro Pro Arg Gly Val Gly Thr		

	25					30					35					
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acc Thr	gac Asp	ccg Pro	ctc Leu	cac His 60	cgc Arg	ttc Phe	cac His	acc Thr	aac Asn 65	agg Arg	tgg Trp	aac Asn	cta Leu	act Thr 70	tct Ser	303
tgt Cys	gga Gly	aca Thr	agt Ser 75	gtt Val	gcc Ala	agc Ser	tca Ser	gaa Glu 80	ggc Gly	agt Ser	gag Glu	gag Glu	ctg Leu 85	ttt Phe	tca Ser	351
tct Ser	gtg Val	tct Ser 90	gtt Val	gga Gly	gat Asp	caa Gln	gat Asp 95	gat Asp	tgc Cys	tat Tyr	tcc Ser	ctg Leu 100	tta Leu	gat Asp	gat Asp	399
cag Gln	gac Asp 105	ttc Phe	act Thr	tct Ser	ttt Phe	gat Asp 110	tta Leu	ttt Phe	cct Pro	gag Glu	ggg Gly 115	agt Ser	gtc Val	tgc Cys	agt Ser	447
gat Asp 120	gtc Val	tct Ser	tct Ser	tct Ser	att Ile 125	agc Ser	act Thr	tac Tyr	tgg Trp	gat Asp 130	tgg Trp	tca Ser	gat Asp	agc Ser	gag Glu 135	495
ttt Phe	gaa Glu	tgg Trp	cag Gln	tta Leu 140	cca Pro	ggc Gly	agt Ser	gac Asp	att Ile 145	gcc Ala	agt Ser	Gly	agt Ser	gat Asp 150	gta Val	543
ctt Leu	tct Ser	gat Asp	gtc Val 155	ata Ile	ccc Pro	agt Ser	att Ile	cca Pro 160	agt Ser	tca Ser	cct Pro	tgc Cys	ctg Leu 165	ctt Leu	cct Pro	591
aaa Lys	aag Lys	aaa Lys 170	aac Asn	aag Lys	cac His	cgg Arg	aat Asn 175	tta Leu	gat Asp	gaa Glu	ctc Leu	cct Pro 180	tgg Trp	agt Ser	gca Ala	639
atg Met	aca Thr 185	aat Asn	gat Asp	gag Glu	cag Gln	gtg Val 190	gaa Glu	tat Tyr	att Ile	gag Glu	tat Tyr 195	Leu	agt Ser	cgg Arg	aaa Lys	687
gtg Val 200	agt Ser	act Thr	gag Glu	atg Met	ggt Gly 205	Leu	cgg Arg	gag Glu	caa Gln	ctt Leu 210	Asp	att Ile	att Ile	aag Lys	atc Ile 215	735
att Ile	gat Asp	cct Pro	tct Ser	gct Ala 220	Gln	atc Ile	tcc Ser	cct Pro	aca Thr 225	Asp	agg Arg	gag Glu	ttt Phe	att Ile 230	att Ile	783
gaa Glu	ctt Leu	aac Asn	tgt Cys 235	Leu	aca Thr	gat Asp	gaa Glu	aaa Lys 240	Leu	aag Lys	cag Gln	gto Val	aga Arg 245	Asn	tat Tyr	831

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927 aga agc aac ttt agt tgt gca agc acc agt gga gtg agc ggt gcc agt Arg Ser Asn Phe Ser Cys Ala Ser Thr Ser Gly Val Ser Gly Ala Ser 275 265 270 975 gcc agc gcc agc agc agt gcc agc atg gtc agt tct gca agc agc Ala Ser Ala Ser Ser Ser Ser Ala Ser Met Val Ser Ser Ala Ser Ser 295 285 290 280 agt ggg tcc agt gtt gga aac tct gct tca aac tcc agt gcc aac atg 1023 Ser Gly Ser Ser Val Gly Asn Ser Ala Ser Asn Ser Ser Ala Asn Met 300 1071 agt cga gca cac agt gac agc aac ctg tct gca agt gca gca gag cgg Ser Arg Ala His Ser Asp Ser Asn Leu Ser Ala Ser Ala Ala Glu Arg 320 1119 att cgg gat tca aaa aag cga tcc aag cag cgg aag tta cag cag aag Ile Arg Asp Ser Lys Lys Arg Ser Lys Gln Arg Lys Leu Gln Gln Lys 335 330 1167 gcc ttc cgc aag agg cag ctg aag gag cag agg cag gcc cgg aag gag Ala Phe Arg Lys Arg Gln Leu Lys Glu Gln Arg Gln Ala Arg Lys Glu 355 350 345 agg ctc agt ggg ctc ttc ctt aac gaa gag gtg ctg tcc ttg aaa gtg 1215 Arg Leu Ser Gly Leu Phe Leu Asn Glu Glu Val Leu Ser Leu Lys Val 370 365 360 act gag gaa gac cat gaa gca gat gtt gat gtt ttg atg taa taagggt 1264 Thr Glu Glu Asp His Glu Ala Asp Val Asp Val Leu Met 385 380 gaatttatca acgttctttg tgagcattaa aatactccat ccttatgggt ttacatgcaa 1324 1335 aaaaaaaaa a

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<211> 2251

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (203)..(1582)

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gatgcaggaa ttcatctaat tttcactgcc gggcgaggtg tgagagccct agcatctgaa 180
agtggtcgac ttgcgagttg tt atg gag aaa act tgt ata gat gca ctt cct 232

						Met 1		ı Lys	Thr	Cys		. Asp) Ala	. Leu	Pro 10	
ctt Leu	act Thr	atg Met	aat Asn	tct Ser 15	tca Ser	gaa Glu	aag Lys	caa Gln	gag Glu 20	act Thr	gta Val	tgt Cys	att Ile	ttt Phe 25	gga Gly	280
act Thr	ggt Gly	gat Asp	ttt Phe 30	gga Gly	aga Arg	tca Ser	ctg Leu	gga Gly 35	ttg Leu	aaa Lys	atg Met	ctc Leu	cag Gln 40	tgt Cys	ggt Gly	328
tat Tyr	tct Ser	gtt Val 45	gtt Val	ttt Phe	gga Gly	agt Ser	cga Arg 50	aac Asn	ccc Pro	cag Gln	aag Lys	acc Thr 55	acc Thr	cta Leu	ctg Leu	376
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ggc Gly 75	atc Ile	ata Ile	atc Ile	ata Ile	gca Ala 80	atc Ile	cac His	aga Arg	gag Glu	cat His 85	tat Tyr	gat Asp	ttt Phe	ctc Leu	aca Thr 90	472
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ctt Leu 65	ctc Leu	agc Ser	gcc Ala	tat Tyr	ggc Gly 70	gag Glu	gtc Val	gga Gly	cgc Arg	gtc Val 75	ttc Phe	ttt Phe	cag Gln	gct Ala	gag Glu 80	240
gac Asp	cgg Arg	ttc Phe	gtg Val	aga Arg 85	cgc Arg	aag Lys	aag Lys	aag Lys	gca Ala 90	gca Ala	gca Ala	gct Ala	gcc Ala	gga Gly 95	gga Gly	288
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cgt Arg	gac Asp	aag Lys 115	cgc Arg	ata Ile	gcc Ala	aag Lys	cgc Arg 120	gtg Val	gcg Ala	gcc Ala	agt Ser	cta Leu 125	cac His	aac Asn	acg Thr	384
cct Pro	atg Met 130	ggt Gly	gcc Ala	cgc Arg	agg Arg	cgc Arg 135	agc Ser	ccc Pro	ttc Phe	cgt Arg	tat Tyr 140	gat Asp	ctt Leu	tgg Trp	aac Asn	432
ctc Leu 145	aag Lys	tac Tyr	ttg Leu	cac His	cgt Arg 150	Phe	acc Thr	tgg Trp	tcc Ser	cac His 155	ctc Leu	agc Ser	gag Glu	cac His	ctc Leu 160	480
gcc	ttt	gag	cgc	cag	gtg	cgc	agg	cag	cgc	ttg	aga	gcg	gag	gtt	gct	528

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tgg aca ttt gcc cag cgt cct act gag cag gaa ctg agg gcc cgt aaa Trp Thr Phe Ala Gln Arg Pro Thr Glu Gln Glu Leu Arg Ala Arg Lys 210 220	672
gca gca cgg cca ggg gga cgt gaa cgg gct cgc ctg gca act gcc cag Ala Ala Arg Pro Gly Gly Arg Glu Arg Ala Arg Leu Ala Thr Ala Gln 225 230 235 240	720
gac aag gcc cgc tcc aac aaa ggg ctc ctg gcc agg atc ttt gga gcc Asp Lys Ala Arg Ser Asn Lys Gly Leu Leu Ala Arg Ile Phe Gly Ala 245 250 255	768
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ceteegeeag eggeeaggea ecageeagae gaegeeageg acceeggeet eteggeggea	180
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aag ctc agc aag aag aag ggc tac aat gtg aac gac gag aaa gcc Lys Leu Ser Lys Lys Lys Gly Tyr Asn Val Asn Asp Glu Lys Ala 5 10 15	284
aag gag aaa gac aag aag gcc gag ggc gcg gcg	332
acc ccg aag gag agt gag ccc cag gcg gcc gca gag ccc gcc gag gcc Thr Pro Lys Glu Ser Glu Pro Gln Ala Ala Ala Glu Pro Ala Glu Ala 40 45 50	380
aag gag ggc aag gag aag ccc gac cag gac gcc gag ggc aag gcc gag Lys Glu Gly Lys Glu Lys Pro Asp Gln Asp Ala Glu Gly Lys Ala Glu 55 60 65	428
gag aag gag ggc gag aag gac gcg gcg gct gcc aag gag gag gcc ccg Glu Lys Glu Gly Glu Lys Asp Ala Ala Ala Ala Lys Glu Glu Ala Pro 70 75 80	476
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ccc ccg aag gcg ccc gag cag gag cag gcg gc	572
ggc ggc gag gcc ccc aaa gct gct gag gcc gcc gcg gcc ccg gcc gag Gly Gly Glu Ala Pro Lys Ala Ala Glu Ala Ala Ala Ala Pro Ala Glu 120 125 130	620
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ccc aaa aag act gag gcg ccc gca gct cct gcc gcc cag gag acc aaa Pro Lys Lys Thr Glu Ala Pro Ala Ala Pro Ala Ala Gln Glu Thr Lys 150 155 160	716
agt gac ggg gcc cca gct tca gac tca aaa ccc ggc agc tcg gag gct Ser Asp Gly Ala Pro Ala Ser Asp Ser Lys Pro Gly Ser Ser Glu Ala 165 170 175	764
gcc ccc tct tcc aag gag acc ccc gca gcc acg gaa gcg cct agt tcc Ala Pro Ser Ser Lys Glu Thr Pro Ala Ala Thr Glu Ala Pro Ser Ser 180 185 190 195	812
aca ccc aag gcc cag ggc ccc gca gcc tct gca gaa gag ccc aag ccg Thr Pro Lys Ala Gln Gly Pro Ala Ala Ser Ala Glu Glu Pro Lys Pro 200 205 210	860
gtg gag gcc ccg gca gct aat tcc gac caa acc gta acc gtg aaa gag Val Glu Ala Pro Ala Ala Asn Ser Asp Gln Thr Val Thr Val Lys Glu 215 220 225	908
tga caag gacagcctat aggaaaaaca ataccactta aaacaatctc ctctctctct	965
ctctctctc ctctatctc ctctctatct cctctctct	1025
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tggaggagcc atctcctgga ggagaaaact cacctg	ggtgg cggaggctcc ccttgtttgt 300
cctcccggag cctggcgtgg ggttcttctg cgggaa	agaga gagtgcgcgc ggagatagca 360
gtgtggaaac gcgcgaggag tcggagggca cgggcgatg ggt ggt ccc ggg acc aag agc ggg gag Met Gly Gly Pro Gly Thr Lys Ser Gly Glu 1 5 10	cct ttg tgt cct ccg tta 464 Pro Leu Cys Pro Pro Leu
ctg tgt aat cag gac aaa gaa acc ttg act Leu Cys Asn Gln Asp Lys Glu Thr Leu Thr 20 25	
cgg atc cag ccg caa agt ctt caa gga gat Arg Ile Gln Pro Gln Ser Leu Gln Gly Asp 35 40	
aaa tta cgc ttc tcc gca caa gac tta gtt Lys Leu Arg Phe Ser Ala Gln Asp Leu Val 50 55	
ttt gct cca gag aat aaa ttg agt acc aca Phe Ala Pro Glu Asn Lys Leu Ser Thr Thr 65 70	
tct tca aac aat gca gtg ata gaa ctg gca Ser Ser Asn Asn Ala Val Ile Glu Leu Ala 85 90	Lys Ser Pro Glu Ser His
gga cat tgg aga gag tgg tat tat ggt gta Gly His Trp Arg Glu Trp Tyr Tyr Gly Val 100 105	
gaa agg tta ttt gtc aat gaa gaa aat gtt Glu Arg Leu Phe Val Asn Glu Glu Asn Val 115 120	
gtc ctg agc tct cca ttc aaa cag tct atg Val Leu Ser Ser Pro Phe Lys Gln Ser Met 130 135	-
att gaa gtt ctt caa gtt act gat aat aag Ile Glu Val Leu Gln Val Thr Asp Asn Lys 145	

ttg caa gaa tgt agt aac tct gat cag cta caa gga aag gag gaa aga Leu Gln Glu Cys Ser Asn Ser Asp Gln Leu Gln Gly Lys Glu Glu Arg 165 170 175	944
gta aat gaa gaa agt cat cta act gaa aag gaa tat ata gaa cat tgt Val Asn Glu Glu Ser His Leu Thr Glu Lys Glu Tyr Ile Glu His Cys 180 185 190	992
aac acc cct aca act gat tct gat tca tct ata gca gtt aaa gca cta Asn Thr Pro Thr Thr Asp Ser Asp Ser Ser Ile Ala Val Lys Ala Leu 195 200 205	1040
caa ata gat agc ttt ggt tta gtt aca tgc ttt caa caa gag tct ctt Gln Ile Asp Ser Phe Gly Leu Val Thr Cys Phe Gln Gln Glu Ser Leu 210 215 220	1088
gat gtt tct caa atg ata ctt gga aaa tct cag caa cct gag tca aaa Asp Val Ser Gln Met Ile Leu Gly Lys Ser Gln Gln Pro Glu Ser Lys 235 230 235 240	1136
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gaa aaa ggt aac tta aac gag tca gta ata act gaa gag aaa gaa aca Glu Lys Gly Asn Leu Asn Glu Ser Val Ile Thr Glu Glu Lys Glu Thr 260 265 270	1232
gat gga gat cac cta tct tca tta ctg aac aaa act acg gtt cac aat Asp Gly Asp His Leu Ser Ser Leu Leu Asn Lys Thr Thr Val His Asn 275 280 285	1280
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aat tot ttg ota tat gat ttg gat taa ttota tataattttg gacttttaaa Asn Ser Leu Leu Tyr Asp Leu Asp * 325	1428
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caa ata gat agc ttt ggt tta gtt aca tgc ttt caa caa gag tct ctt Gln Ile Asp Ser Phe Gly Leu Val Thr Cys Phe Gln Gln Glu Ser Leu 165 170 175	944
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ata cct gga ttc gac agc ata aaa gaa acc aat atg cag gat ggt agt Ile Pro Gly Phe Asp Ser Ile Lys Glu Thr Asn Met Gln Asp Gly Ser 245 250 255	1184
gtg cag gtc att aaa gat cat gtg acc aat tgt gca ttc agt ttt cag Val Gln Val Ile Lys Asp His Val Thr Asn Cys Ala Phe Ser Phe Gln 260 265 270	1232
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Gln Phe Val Gln Gly Leu Glu Lys Glu Phe Ser Ala Ala Trp Pro Arg 185 190 195 200	
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gat ggc cta gca cgt gga att cgc gaa gct gcc aaa gcc tta gac aag Asp Gly Leu Ala Arg Gly Ile Arg Glu Ala Ala Lys Ala Leu Asp Lys 30 35 40	324
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attotagaac acattateac ettittaaat aageaaaatg atgateecag gitaaaaaac ettiggitaaaa actggitett aagaaceeca agitegeeaa aagaaggite aagetaataa aggaaacite tiggitaecaa tiecatetge eteettetea gitgaeteetg aegagetget eatitaeaca eacetgetee eaceeceace ecacagietg gatigegaaa eetaeegeac eceaceeca gigeaggaag aaggigaece tiggitetgggg tiggigaeaga gagietiggga giggiggiggiggiggiggiggiggiggiggiggiggig	120 180 240 300 360 420
attetagaac acattateac ettittaaat aageaaaatg atgateecag gitaaaaaac ettiggtaaaa actggitett aagaaceeca agitegeeaa aagaaggite aagetaataa aggaaacite tiggitaecaa tiecatetge eteettetea gitgaeteetg aegagetget eatitaeaca eacetgetee eaceeceace eeacagietg gatigegaaa eetaeegeac eecaeeceea gigeaggaag aaggigaeee tiggitetgggg tiggigaeaga gagietiggga giggiggiggiggiggiggiggiggiggiggiggiggig	120 180 240 300 360 420 480
attctagaac acattatcac ctttttaaat aagcaaaatg atgatcccag gttaaaaaac cttggtaaaa actggttctt aagaacccca agttcgccaa aagaaggttc aagctaataa aggaaacttc tggttaccaa ttccatctgc ctccttctca gtgactcctg acgagctgct catttacaca cacctgctcc cacccccacc ccacagtctg gattgcgaaa cctaccgcac cccaccccca gtgcaggaag aaggtgaccc tggtctgggg tggggacaga gagtctggga gggggtggtg gctggcagtc tcggtggctg gcgacgcctc ttccgctctt ccttcctggg aggaggcggg caaggcgaag cctctccgct cagtcgatgg tttccttcag gacgtctcat agaggtgtgg gtgagatccc aggtctgggc cgcaatttct agccacgctg cccaaccttc aggcaagcag tcaggttcca cagctacccc accacctct cagagtcgag gggaacaaga	120 180 240 300 360 420 480 540

ggcaagtgag agccggacgg gcactgggcg actctgtgcc tcgctgagga aaaataacta

aac	Me				y Ası						g Gl				a tca Ser 15	828
														aag Lys 30		876
	_	-		-								_	_	tca Ser		924
		_		-		-							_	gat Asp	-	972
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_				_	_									cgc Arg 110		1116
														gcg Ala		1164
														cag Gln		1212
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-	_		_	_			-		_		_			gga Gly		1308
-	_	_	_		_			-	_	-			-	gat Asp 190		1356
-	-													gaa Glu		1404
~	_	_	_	_	_	-	_	_		_	_	-		gcg Ala		1452

ttt ttt ttt tct tgt cta taa ag catttaaccc ccctgttaca caactcactc Phe Phe Phe Ser Cys Leu * 225 230	1505
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gtcttttttt gtatagttaa cacactaccg aatgtgtctt tagatagccc tgtcctggtg	1625
gtattttcaa tagccactaa ccttgcctgg tacagtatgg gggttgtaaa ttggcatgga	1685
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gccctgagac atttttggcg ccggccccag cctgagcggg gacggcggcc gggagggcgc	240
ggcccgggtt cccgttcccc gcggagcc atg cgg tac aac gag aag gag ctg Met Arg Tyr Asn Glu Lys Glu Leu 1 5	292
cag gct ctg tcc cgg cag ccg gcc gag atg gcg gcc gag ctg ggc atg Gln Ala Leu Ser Arg Gln Pro Ala Glu Met Ala Ala Glu Leu Gly Met 10 15 20	340
agg ggc ccc aag aag ggc agc gtg ctg aag cgg cgg ctg gtg aag ctg Arg Gly Pro Lys Lys Gly Ser Val Leu Lys Arg Arg Leu Val Lys Leu 25 30 35 40	388
gtg gtg aat ttc ctc ttc tac ttt cgg aca gac gag gcc gag ccc gtc Val Val Asn Phe Leu Phe Tyr Phe Arg Thr Asp Glu Ala Glu Pro Val 45 50 55	436
gga gcc ctg ctg ctg gag cgc tgc aga gtc gtc cgg gaa gag ccc ggc	

acc ttc tcc atc agc ttc att gag gac cct gag agg aag tat cac ttt Thr Phe Ser Ile Ser Phe Ile Glu Asp Pro Glu Arg Lys Tyr His Phe 75 80 85	532
gag tgc agc gag gag cag tgt cag gag tgg atg gag gct ctg cgt Glu Cys Ser Ser Glu Glu Gln Cys Gln Glu Trp Met Glu Ala Leu Arg 90 95 100	580
cgg gcc agc tac gag ttc atg cgg aga agc ctc atc ttc tac agg aac Arg Ala Ser Tyr Glu Phe Met Arg Arg Ser Leu Ile Phe Tyr Arg Asn 105 110 115 120	628
gaa atc cgg aag gtg acg ggc aag gac ccc ctg gaa cag ttc ggc ata Glu Ile Arg Lys Val Thr Gly Lys Asp Pro Leu Glu Gln Phe Gly Ile 125 130 135	676
tcc gag gag gcc agg ttc cag ctg agt ggc ttg cag gcg tga gcgcagg Ser Glu Glu Ala Arg Phe Gln Leu Ser Gly Leu Gln Ala * 140 145 150	725
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catgcctgga tctgttttgt tttggttttt ggtttttggg tcagggtttc actgtgttgc	845
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att tac tgc tc Ile Tyr Cys Se 5	-										
ttt gag ggc tg Phe Glu Gly Tr 65											
ttt gtg acc cg Phe Val Thr Ar 80				g Leu Met Asp	=						
gac ccc tgg aa Asp Pro Trp Ly 95											
ccc aaa gtc aa Pro Lys Val As					e Cys						
ggc ctc ccc ag Gly Leu Pro Se 13	er Phe Ser										
ccg ggg ctg ga Pro Gly Leu Gl 145											
tgc ccc gag cg Cys Pro Glu Ar 160	g Gly Ser	-	-	u Asp Asp Ala							
ctg tgg ggg ga Leu Trp Gly Gl 175											
ctg tcc atg tg Leu Ser Met Cy					Ala						
ccg tcg gct gc Pro Ser Ala Al 21	a Pro Glu										

cgg tcg gtg cta tgc cag gag gtg gag gtg gcc atc ccc tta ccc gcc Arg Ser Val Leu Cys Gln Glu Val Glu Val Ala Ile Pro Leu Pro Ala 225 230 235	722
cgc tcc ctg ctg gtc ctc acc ggg gcg gca cgg cac cag tgg aag cat Arg Ser Leu Leu Val Leu Thr Gly Ala Ala Arg His Gln Trp Lys His 240 245 250	770
gcc atc cac cgc aga cac atc gag gcc cgc cgc gtc tgc gtc act ttc Ala Ile His Arg Arg His Ile Glu Ala Arg Arg Val Cys Val Thr Phe 255 260 265 270	818
cgg gag ctg tcg gct gag ttt ggc cct gga ggg agg cag caa gag ctg Arg Glu Leu Ser Ala Glu Phe Gly Pro Gly Gly Arg Gln Gln Glu Leu 275 280 285	866
ggc cag gaa ctg ctg cgg atc gcc ctc tcc ttc cag gga aga ccc gtg Gly Gln Glu Leu Leu Arg Ile Ala Leu Ser Phe Gln Gly Arg Pro Val 290 295 300	914
tga accg cctccttggc tccagacttg actgatcccg ggattgaaat gaggagcaca *	971
gaacagggcc tcctgcaact cacggggttt caagagaaga tggctgaccc ctgatgctgt	1031
gagcagtgtg agccctgccc aggagcaggt tttgatggga acgtacctcc aggcagcccc	1091
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cac ttc ata gct tcg ggg atg gtc aat cag gag atg tta aac atg tct His Phe Ile Ala Ser Gly Met Val Asn Gln Glu Met Leu Asn Met Ser 25 30 35	150

_					tgt Cys											-	198
					gaa Glu								_	_		2	246
					gat Asp 75											2	294
_	_	_	_		act Thr	_		-	_				_	-		3	342
	_			_	aga Arg					-						;	390
-	_	-			cct Pro		-	_	-			-		_	_	2	438
	_	_		_	gct Ala						_		-			2	486
	-			_	aat Asn 155					_	-			-		Ţ	534
-		_	_		gca Ala	_	-	-		_					_		582
_	_	_	-		ata Ile											•	530
_		_			aaa Lys			_	•	_	_					(678
					cct Pro											•	726
		att Ile		_	aag Lys 235	tag *	tc a	atcaa	actt	ta tt	ctttg	gctta	a att	tatgt	igta		779
gtca	atato	gaa g	gtcta	attto	ct ag	gttga	actgt	c aac	catgo	ggta	ttaa	atagt	ct t	tgct	gctgg	{	339
taa	tacto	gaa a	agaad	cctgo	et tt	tatat	tgga	a gta	atcaa	agat	ctca	aggtt	ca t	ttaag	gaccaa	8	399

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gaa gaa ctg gca gag aat ata ctc aag tgg cgt aaa caa caa aac gaa Glu Glu Leu Ala Glu Asn Ile Leu Lys Trp Arg Lys Gln Gln Asn Glu 150 165	534
gtt tcg tct tgt atc ccc aaa ata tta gct gaa gaa agt tat ctt tat Val Ser Ser Cys Ile Pro Lys Ile Leu Ala Glu Glu Ser Tyr Leu Tyr 170 175 180	582
aaa cat gat att ata atg cct cct tta cct ttt act tct aaa gtt cat Lys His Asp Ile Ile Met Pro Pro Leu Pro Phe Thr Ser Lys Val His 185 190 195	630
gtc caa act att aat gcc aag tag tcatcaactt tatttttgct taattatgtg Val Gln Thr Ile Asn Ala Lys * 200 205	684
tagtcatatg aagtctattt ctagttgact gtaacatggg tattaatagt ctttgctgct	744
ggtaatactg aaagaacctg ctttatattg gagtatcaag atctcaggtt cattaagacc	804
aaactgactt ttcctttgtt tttcatatat ttttattcta cctttcagta aaactagaga	864
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ggggtggtga ggcccgaggc agctcttgtt cagcttctgg aatttctgag cagccctcgt	180
cagtacaag atg gac ccc gta gtc ttg agt tac atg gac agt cta ctg Met Asp Pro Val Val Leu Ser Tyr Met Asp Ser Leu Leu 1 5 10	228
cgg caa tca gat gtc tca cta ttg gat ccg cca agc tgg ctc aat gac Arg Gln Ser Asp Val Ser Leu Leu Asp Pro Pro Ser Trp Leu Asn Asp 15 20 25	276
cat att att ggg ttt gcg ttt gag tac ttt gcc aac agt cag ttt cat His Ile Ile Gly Phe Ala Phe Glu Tyr Phe Ala Asn Ser Gln Phe His 30 35 40 45	324

gac tgc tct gat cac gtc agt ttc atc agc cct gaa gtc acc cag ttc Asp Cys Ser Asp His Val Ser Phe Ile Ser Pro Glu Val Thr Gln Phe 50 55 60	372
atc aag tgc act agc aac cca gca gag att gcc atg ttc ctt gaa cca Ile Lys Cys Thr Ser Asn Pro Ala Glu Ile Ala Met Phe Leu Glu Pro 65 70 75	420
ctg gac ctc ccc aac aag aga gtt gta ttt tta gcc atc aat gat aac Leu Asp Leu Pro Asn Lys Arg Val Val Phe Leu Ala Ile Asn Asp Asn 80 85 90	468
tcc aac cag gca gct gga gga acc cac tgg agt tta ttg gtc tac ctc Ser Asn Gln Ala Ala Gly Gly Thr His Trp Ser Leu Leu Val Tyr Leu 95 100 105	516
caa gat aaa aat agc ttt ttt cat tat gat tcc cat agc agg agc aac Gln Asp Lys Asn Ser Phe Phe His Tyr Asp Ser His Ser Arg Ser Asn 110 125	564
tca gtt cac gca aag cag gta gca gag aaa ctg gag gct ttc tta ggc Ser Val His Ala Lys Gln Val Ala Glu Lys Leu Glu Ala Phe Leu Gly 130 135 140	612
aga aaa gga gac aaa ctg gcc ttt gtg gaa gag aaa gcc cct gcc caa Arg Lys Gly Asp Lys Leu Ala Phe Val Glu Glu Lys Ala Pro Ala Gln 145 150 155	660
caa aac agc tat gac tgt ggg atg tac gtg ata tgt aac act gag gcc Gln Asn Ser Tyr Asp Cys Gly Met Tyr Val Ile Cys Asn Thr Glu Ala 160 165 170	708
ttg tgt cag aac ttc ttt agg caa cag aca gaa tca ctg ctg cag cta Leu Cys Gln Asn Phe Phe Arg Gln Gln Thr Glu Ser Leu Leu Gln Leu 175 180 185	756
ctc acc cct gca tac atc aca aag aag agg gga gaa tgg aaa gat ctc Leu Thr Pro Ala Tyr Ile Thr Lys Lys Arg Gly Glu Trp Lys Asp Leu 190 195 200 205	804
att gcc aca ctt gct aaa aag tag ctattgaagt atatttgcga cttttgaagg Ile Ala Thr Leu Ala Lys Lys * 210	858
ctcctctttc tgcccttccc catttgttgg atggctgcaa tctcagtgcc tgagggaaga	918
tgcctagtag aggaaagctt aatactcttt ttcctgaaag aatatcatcc tctgcattat	978
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_	tcc Ser				_		-									161
	gaa Glu	-				_						_				209
	tgt Cys	_	_	-												257
_	tca Ser 55					_										305
	gat Asp		_		_	_	_									353
	gca Ala		-													401
	agc Ser															449
_	cgc Arg				_	_	_		-							497
	gag Glu 135															545
	gaa Glu															593
	atc Ile															641

ttg g Leu G																689
ctc a Leu L																737
ttg g Leu G 2	_				_	_	_		_	_		_	_	_		785
acg g Thr V 230	-				_					_		_	-	-		833
aca a Thr A																881
gac c Asp G		_					_		_		_	_	_			929
atg g Met A	la	_	_	_	_	_				_			_			977
tcg g Ser A 2																1025
cta g Leu G 310	-				_	_		_	_	_				_	_	1073
aag a Lys A		-			-	-			-							1121
ctg g Leu G								_	_				_			1169
gtg g Val A	4sp		-	_	_			-				_			_	1217
atg c Met H 3						_			_	_		-		_	-	1265
ctg a Leu M 390	_		-	_	-				_	_		_	_	_		1313

						cac His										13	361
-					_	aag Lys	_		_	_	_		_		_	14	109
						tct Ser										14	157
						atg Met 460										15	505
	-	_		_		ccc Pro				_	_		-		_	15	553
			-	-	-	att Ile			_	_	-	_	_	_	_	16	501
						cag Gln	-	-	-			-			-	16	549
						cgc Arg										16	597
						acc Thr 540										17	745
						att Ile										17	793
		_			-	gcc Ala		_	_	_		_		_		18	341
						tgc Cys										18	889
	-		-	_	_	gca Ala	-	_		_	_					19	37
						gaa Glu 620										19	85
cta	aaa	gtg	gag	cag	aaa	ctg	gag	cag	att	aaa	aag	gtg	cag	aaa	gtg	20	33

Leu 630	Lys	Val	Glu	Gln	Lys 635	Leu	Glu	Gln	Ile	Gly 640	Lys	Val	Gln	Gly	Val 645	
	_				cac His	_	_	_	_		_					2081
-					agc Ser											2129
		•	_		gtg Val			_						_	_	2177
	_	_	_		cct Pro	_			_	_		_	_	-		2225
	_	_			ctt Leu 715		-			_			_			2273
					cag Gln											2321
_		_			cag Gln	_		-		-		_				2369
_		_		-	ggc Gly		_		-	-		-	_		_	2417
					ctc Leu		_		_	_				_	_	2465
					aac Asn 795											2513
_	_		-	-	cag Gln		-					_		_		2561
_	-			_	gca Ala	_			-							2609
_		-	-		cac His	_		-	-			-	-	-		2657
			-		gca Ala			_				_	-	_		2705

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1085

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acc ggt ctg ata gaa gtc tgg ata atc ctg ctg gag Thr Gly Leu Ile Glu Val Trp Ile Ile Leu Leu Glu 1110 1115 1120	0 0
gct gtg tcc aat tgt cca cgg cag cac caa cca cca Ala Val Ser Asn Cys Pro Arg Gln His Gln Pro Pro 1130	
ctc ttt gag ctg ttg aga gat gtg acg aaa aca cca Leu Phe Glu Leu Leu Arg Asp Val Thr Lys Thr Pro 1145 1150	
ggt atc tat gca gtg gtt cac ctc ctc ctt cct gtg Gly Ile Tyr Ala Val Val His Leu Leu Leu Pro Val 1160 1165 1	
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acc atg ctg aag gac ctc ttt gag ttg ctg gtc gcc Thr Met Leu Lys Asp Leu Phe Glu Leu Leu Val Ala 1225 1230	
ccc act gaa acc atc tcc aga gtg ggc tgc tcc tgt Pro Thr Glu Thr Ile Ser Arg Val Gly Cys Ser Cys 1240 1245 1	-
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gac ctg ctg ggc tgc ttc cac agc ggc acg gag agc Asp Leu Leu Gly Cys Phe His Ser Gly Thr Glu Ser 1290 1295	
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	gag Glu					Arg					Gln					4097
Asp	acc Thr 1335	_	_		Pro	_				Asn		_		_	_	4145
	tgc Cys	_		Ile			_		Pro	_	_			Asn		4193
	acc Thr	_	Lys	_				Arg	-				Ser	_	_	4241
	cat His	Gln				-	Asn			_		Leu		-	-	4289
	gtc Val					Pro					Thr					4337
Glu	gcc Ala 1415				Gly					Ile						4385
	gtc Val			Asp					Ser					Arg		4433
	gac Asp		Ser			_	_	Cys	_	_	_		Val			4481
	ggg Gly	Gly					Tyr					Met				4529
	tat Tyr					Val					Thr					4577
Ile	acg Thr 1495	_			Val	_	_	-		Phe		_	-		_	4625
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	gaa Glu		Ala					Pro					Lys			4721
tgg	cgg	gca	cgg	atg	ccc	ttg	ctc	agc	gtc	cag	cct	gtc	agc	aac	gca	4769

Trp	Arg		Arg 1545	Met	Pro	Leu		Ser 1550	Val	Gln	Pro		Ser L555	Asn	Ala	
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Сув	aac Asn 1575				Gln	_		_	_	Leu			_	_		4865
	cct Pro			Phe					Phe					Ser		4913
-	tcc Ser		Ser					Thr					Gly		-	4961
	cct Pro	Ser		-	-	-	Ser	_				His	_			5009
	ctg Leu	_	_	_	-	Gly			-	_	Leu	_			_	5057
Pro	aaa Lys 1655				Lys					Lys						5105
	gcg Ala			Lys				_	Āla	-	-	_		Ile		5153
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	ttc Phe	Pro					Val					Glu				5249
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Asp	caa Gln 1735			_	Arg				_	Āla				_	_	5345
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	tcg Ser															5441

1770 1775 1780

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acg gcc ctc cag ccc gca gtg ttc ccg tgc atc agt cag ctg acc tgt Thr Ala Leu Gln Pro Ala Val Phe Pro Cys Ile Ser Gln Leu Thr Cys 1800 1805 1810	5537
cac gtg acc gac atc aga gtt cgc cag gct gtg agg gag tgg ctg ggc His Val Thr Asp Ile Arg Val Arg Gln Ala Val Arg Glu Trp Leu Gly 1815 1820 1825	5585
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387

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<220>

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<400> 171

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218 cat aga cct ggt gga agg cgt ggc gcc ctg acc cag gga ttt ggc His Arg Pro Gly Gly Arg Arg Gly Ala Ala Leu Thr Gln Gly Phe Gly 15 25

tcc tgt agc gct gct ggg cag agg tcc gca gga gct gca ggt act tct 266 Ser Cys Ser Ala Ala Gly Gln Arg Ser Ala Gly Ala Ala Gly Thr Ser 30 35

tgg cca act cta gct gct gct tct tgc act gct tcc ggc ggg gtg agg Trp Pro Thr Leu Ala Ala Ala Ser Cys Thr Ala Ser Gly Gly Val Arg 45 50 55	314
acc cac agc tct gat gtg ggc gct tca ggc cat ggt gga gct gag att Thr His Ser Ser Asp Val Gly Ala Ser Gly His Gly Gly Ala Glu Ile 60 65 70	362
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15 20 25	
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_	acc Thr					-				_		_	_			2:	90
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-	gtc Val 110		-	-		_	_	_	_					_		31	86
	cct Pro		_	_	-	-		-	_		_				_	43	34
	cct Pro															48	82
	cct Pro															53	30
	gac Asp															5	78
	agg Arg 190															62	26
	ctg Leu															67	74
_	tgg Trp							-	_		_	_	_	-	-	72	22
	gag Glu	_	-													71	70
	gac Asp															81	18
_	aag Lys 270		_	_							-					86	56

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att gag aag ctg ggc ctc cag agg aag aag tcc aag ttc cgc ttg tcc Ile Glu Lys Leu Gly Leu Gln Arg Lys Lys Ser Lys Phe Arg Leu Ser 320 325 330	1010
aag atc tgg tca cca aaa agc aaa agc ccc tcc cag tag tagccag Lys Ile Trp Ser Pro Lys Ser Lys Ser Ser Pro Ser Gln * 335 340 345	1059
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ttcggctttg atg acc tta atc cag gca aat cct aaa tcc tat cca gtc Met Thr Leu Ile Gln Ala Asn Pro Lys Ser Tyr Pro Val 1 5 10	169
ggc agc atc cag atg aac cac aac tcc ttc ctc agc gca acc agg cca Gly Ser Ile Gln Met Asn His Asn Ser Phe Leu Ser Ala Thr Arg Pro 15 20 25	217
agg gag tgc tcc atc ccc tgc ctc gca gtt act gat tct cca agc cgg Arg Glu Cys Ser Ile Pro Cys Leu Ala Val Thr Asp Ser Pro Ser Arg 30 35 40 45	265
gcg ccg ccc agt cct ggc ggg gct tcc ccc acc cct ctc cgc gcc ggg Ala Pro Pro Ser Pro Gly Gly Ala Ser Pro Thr Pro Leu Arg Ala Gly 50 55 60	313

								gtg Val 70			Trp					361
											gtc Val					409
											gct Ala 105					457
											agc Ser			tag *	ccg	505
agto	cgag	gca (gcac	ggtto	dd da	aaggo	cagco	c aag	ggatg	gege	С					546
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		ccc		atα	caa	gac	acc	gac					taa	~~~	~~~	
	GIII	Pro 5			Gln	Asp					gcg Ala					103
	ggc	5 cgg	Gln gca	Met ggc	ggg	cca	Ala 10 ccg	Asp cag	Glu gtc	Pro gcc		Asp 15 gcc	Ser cag	Gly gcg	Gly gcg	103 151
Glu tgc	ggc Gly 20 agc	5 cgg Arg	Gln gca Ala gac	Met ggc Gly cgc	ggg Gly atg	cca Pro 25	Ala 10 ccg Pro	Asp cag Gln ctc	Glu gtc Val ctc	Pro gcc Ala agg	Ala ggc Gly	Asp 15 gcc Ala aga	Ser cag Gln gca	Gly gcg Ala cag	Gly gcg Ala aca	
tgc Cys 35	ggc Gly 20 agc Ser	5 cgg Arg gag Glu	gca Ala gac Asp	ggc Gly cgc Arg	ggg Gly atg Met 40	cca Pro 25 acc Thr	Ala 10 ccg Pro ctg Leu aaa	Asp cag Gln ctc Leu	gtc Val ctc Leu	gcc Ala agg Arg 45	Ala ggc Gly 30 ctg	Asp 15 gcc Ala aga Arg	Ser cag Gln gca Ala	gcg Ala cag Gln	Gly gcg Ala aca Thr 50 gaa	151
tgc Cys 35 aaa Lys	ggc Gly 20 agc Ser caa Gln	cgg Arg gag Glu caa Gln	Gln gca Ala gac Asp ctc Leu gaa	Met ggc Gly cgc Arg tta Leu 55 caa	ggg Gly atg Met 40 gaa Glu	cca Pro 25 acc Thr tat Tyr	Ala 10 ccg Pro ctg Leu aaa Lys caa	Asp cag Gln ctc Leu tca Ser	gtc Val ctc Leu atg Met 60	gcc Ala agg Arg 45 gtt Val caa	ggc Gly 30 ctg Leu	Asp 15 gcc Ala aga Arg gca Ala	Ser cag Gln gca Ala agt Ser gct	Gly gcg Ala cag Gln gaa Glu 65 aaa	Gly gcg Ala aca Thr 50 gaa Glu att	151 199

	_	ctt Leu	-		-		_	_				_				391
		gag Glu														439
		cta Leu								-			-	-	-	487
		gat Asp			-		_		-		_	_	_	_	_	535
		aaa Lys 165														583
		aaa Lys														631
		atc Ile														679
		caa Gln								-		-		_		727
		gag Glu														775
	_	gac Asp 245	_	_	taa *	taag	gaa t	tcat	ttct	g ac	catat	ttta	a cat	ttct	ggc	829
aato	ctcaa	act o	ttat	ttgg	ga at	actt	ctgt	gca	ittte	gtct	gtco	cacco	gta a	atttt	agaaa	889
agca	atato	cca t	aacg	gttta	ac ag	ıttgt	agta	a cag	gttgt	ggt	tagt	tatt	tg t	agto	ggatt	949
gaaa	agtaa	att t	tttt	cttt	it ta	ıtatt	tcta	a tat	tcag	ıgtt	ggtt	tttt	.gg t	gaag	ıttaga	1009

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95

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gca aac gcc ttc aac agc att att cca gaa gac acc ttc ttc ccc

674

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Pro 210 215 220	
agc cca gaa agt tcc tgt gat gtc aag ctg gtc gag aaa agc ttt gaa Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu 225 230 235	722
aca gat acg aac cta aac ttt caa aac ctg tca gtg att ggg ttc cga Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg 240 245 250	770
atc ctc ctc ctg aaa gtg gcc ggg ttt aat ctg ctc atg acg ctg cgg Ile Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg 255 260 265	818
ctg tgg tcc agc tga g Leu Trp Ser Ser * 270	834
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Met Arg Ile Arg Leu Cys 1 5	
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acc cag gca cca aca tct cag atc ctg gca gca gga cgg cgc atg aca Thr Gln Ala Pro Thr Ser Gln Ile Leu Ala Ala Gly Arg Arg Met Thr 25 30 35	150
ctg aga tgt acc cag gat atg aga cat aat gcc atg tac tgg tat aga Leu Arg Cys Thr Gln Asp Met Arg His Asn Ala Met Tyr Trp Tyr Arg 40 45 50 55	198
caa gat cta gga ctg ggg cta agg ctc atc cat tat tca aat act gca Gln Asp Leu Gly Leu Gly Leu Arg Leu Ile His Tyr Ser Asn Thr Ala 60 65 70	246

						~	-		~			_	-	tcc Ser	-	294
			-	-				_	_			-	_	ccc Pro		342
_						_	_	-	_	_		_	_	ggg Gly	_	390
														acc Thr		438
_		_	_			-				-	~	_		ttt Phe 150		486
		-								_	_		_	gtg Val	_	534
-							gac Asp 175				_	_	tga *	tttt	ttc	583
atag	gacta	atg a	agctt	ctaa	aa aa	atca	atcco	cat	atto	gtc	atta	acatt	ct t	ggga	atcaaa	643
tata	actgo	cat c	gaaaa	aaaga	at go	ctcaç	gaaaa	gto	ctato	gtta	agtt	taato	gta g	gaata	atatga	703
atga	agtga	ag g	gaaag	gtgtt	t to	gaaac	ccato	ata	ıggga	ata	taat	aaga	ata a	natt	acact	763
agaa	taaa	at c	raaac	:												778

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cacccctgca ggagaggctt ggggtgagtt ttgggaataa ggaccatcca gccac atg
Met
1

_	_		_	-										caa Gln		226
														cgc Arg		274
	_						-	-		-		_		cag Gln		322
-		_	_			_			_	_			-	aag Lys		370
														aag Lys 80		418
	_			_					_					caa Gln		466
			gga Gly					tga *	gcto	ga gg	ggaag	ggata	a gga	atttg	ggag	518
agct	gaca	att c	tgat	gago	g go	etteg	gtta	a aag	gctca	acaa	aaac	cctt	ccc c	ctccc	ccatg	578
ccct	ttga	aa t	catt	tgaa	at ca	aaga	ttgc	gtg	gtgtt	caaa	gaca	atgtt	tg t	ctgt	tatct	638
gaaa	gcto	gtg g	gtttc	ctctt	t aa	caga	ittca	a ggg	gaata	catc	cttt	gact	cg g	gacca	agaag	698
gaat	tato	gag														708

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<213> Homo sapiens

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<221> CDS
<222> (120)..(1175)

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<222> (1)...(1463)
<223> n = a,t,c or g
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					cca Pro											215
					cac His											263
					ggc Gly											311
					cct Pro 70											359
					ctg Leu											407
aca Thr	gly ggg	acc Thr	cca Pro 100	gaa Glu	ccg Pro	ctt Leu	gac Asp	cca Pro 105	cag Gln	ggt Gly	tca Ser	ctc Leu	agc Ser 110	ctc Leu	agc Ser	455
					ctt Leu											503
					gac Asp											551
					att Ile 150				Gly		Lys			Lys		599
					gtg Val											647
					aca Thr											695
					agc Ser											743
					agc Ser											791

cct ggc cac gag ttc ctg ctg cag tcg gac cac gag aca gag ctg cgaPro Gly His Glu Phe Leu Leu Gln Ser Asp His Glu Thr Glu Leu Arg225230	839
gcc tgg cac cgc gcg ctg cgg act gtc atc gag cgg ctg gat cgg gag Ala Trp His Arg Ala Leu Arg Thr Val Ile Glu Arg Leu Asp Arg Glu 245 250 255	887
aac ccc ctg gag ctg cgt ctg tcg ggc tct gga ccc gcg gag ctg agcAsn Pro Leu Glu Leu Arg Leu Ser Gly Ser Gly Pro Ala Glu Leu Ser260265	935
gcc ggg gag gac gaa gaa gag gag tcg gag ctg gtg tcc aag ccg ctg Ala Gly Glu Asp Glu Glu Glu Glu Ser Glu Leu Val Ser Lys Pro Leu 275 280 285	983
ctg cgc ctc agc agc cgc cgg agc tcc att cgg ggg ccc gaa ggc acc Leu Arg Leu Ser Ser Arg Arg Ser Ser Ile Arg Gly Pro Glu Gly Thr 290 295 300	1031
gag cag aac cgc gtg cgc aac aaa cta aag cgg ctc atc gcg aag aga Glu Gln Asn Arg Val Arg Asn Lys Leu Lys Arg Leu Ile Ala Lys Arg 305 310 315 320	1079
ccg ccc tta caa agc ctg cag gag cgg ggt ctg ctc cga ggt gag ggg Pro Pro Leu Gln Ser Leu Gln Glu Arg Gly Leu Leu Arg Gly Glu Gly 325 330 335	1127
gct ggg cca ggt tca tgg ata aga aaa ctc cag cga ggc tca gag tag Ala Gly Pro Gly Ser Trp Ile Arg Lys Leu Gln Arg Gly Ser Glu * 340 345 350	1175
agcttcccag aactagacca caaccttctg tgactgctgc tttcccacta ccccagattg	1235
tttaggggag aagctggggt gacctgtacc cctttgccag attgtttgaa gcangggaag	1295
ggaggtggag tgtatttcct tgcccaggcc tggcacaggc agccaggagg accagcctca	1355
cttaaggata aagacctatg ctgagaagag ctcctgtgag tgacgctggc acttggcttc	1415
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<211> 678

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a atg tgc aca ctt gca tgt gtg cac aca cat aca cac act ctc ata Met Cys Thr Leu Ala Cys Val His Thr His Thr His Thr Leu Ile 1 5 10 15	166
tac cta aaa tac gaa tgg gag cac atg aca cac aca ttc tgc ctg ctg Tyr Leu Lys Tyr Glu Trp Glu His Met Thr His Thr Phe Cys Leu Leu 20 25 30	214
ctt tgt ctg tgc ata att tta tct tcc agg tca tct gtg ctg gtg tct Leu Cys Leu Cys Ile Ile Leu Ser Ser Arg Ser Ser Val Leu Val Ser 35 40 45	262
atc agt ctg cta gtc ttt ccc cgc cat gtg gcc att gtt cca gtc ccc Ile Ser Leu Leu Val Phe Pro Arg His Val Ala Ile Val Pro Val Pro 50 55 60	310
tcc tat gca cac cca ggt ttc tct agg acc atg tta tcc cag agc cag Ser Tyr Ala His Pro Gly Phe Ser Arg Thr Met Leu Ser Gln Ser Gln 65 70 75	358
gtg gac agg aca caa agg gct agg ggt caa tgg ggg tgt tct cgc ctc Val Asp Arg Thr Gln Arg Ala Arg Gly Gln Trp Gly Cys Ser Arg Leu 80 85 90 95	406
cag tct gcc ctg cca gcc ccc agt cgt ggg tgg acc tgc cat cag ctt Gln Ser Ala Leu Pro Ala Pro Ser Arg Gly Trp Thr Cys His Gln Leu 100 105 110	454
gct ctg ccc act ccc cag gcc tga gctgctggcg aaacaggcaa gtgactgcac Ala Leu Pro Thr Pro Gln Ala * 115	508
tgcccatggc cggtcaccag cctcaggtga accccaggag gggttcctac ctagcactca	568
tcatttcctc aacttcacta ctgtgtcgcc ctgtgggaca gggaagtcca agtcggggaa	628
aaagcctgtg gggaggggtt ggtgggagat ggggagccca tatggcccag	678

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<211> 599

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<213> Homo sapiens

<220>

<221> CDS

<222> (189)..(512)

<400> 180

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ccactgaatt gtatagaggc ggagtctcgg gtgcattcaa gatccggctt cactcgtaac	180
ccactgcc atg gcc gag gaa ggc agt gct gct gga ggt gta atg gac att Met Ala Glu Glu Gly Ser Ala Ala Gly Gly Val Met Asp Ile 1 5 10	230
aat act gtt tta cag gag gtg ctg aag acc gcc ctc atc cat gat ggc Asn Thr Val Leu Gln Glu Val Leu Lys Thr Ala Leu Ile His Asp Gly 15 20 25 30	278
cta gca tat gaa att tgc aaa gct gcc aaa gcc tca gac aag tgc caa Leu Ala Tyr Glu Ile Cys Lys Ala Ala Lys Ala Ser Asp Lys Cys Gln 35 40 45	326
gcc cat ctt tgt gtg ctg tgt gtg ctt gca tcc aac tgt gat gag cct Ala His Leu Cys Val Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro 50 55 60	374
atg tat gtc aag ttg gtg gag gcc ctt tgt gct gaa cac caa atc aac Met Tyr Val Lys Leu Val Glu Ala Leu Cys Ala Glu His Gln Ile Asn 65 70 75	422
cta att aag gtt gat gac cag aaa cta ggg gaa tcg gta ggc ctc tgt Leu Ile Lys Val Asp Asp Gln Lys Leu Gly Glu Ser Val Gly Leu Cys 80 85 90	470
aaa act gac aga gag ggg aaa ccg tgt aaa gtg gtt ggt tga agttgta Lys Thr Asp Arg Glu Gly Lys Pro Cys Lys Val Val Gly * 95 100 105	519
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aatgcaagaa atgaacaagt	599
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acc gac cag ccg cac acg cag cgc cag gag ata ctg gcc aag tac Thr Asp Gln Pro His Thr Gln Arg Arg Lys Glu Ile Leu Ala Lys Tyr 15 20 25 30	157

	gcc Ala															205	5
	ctg Leu															253	3
	ctg Leu															301	1
	gtg Val 80															349	Э
	gcc Ala															391	7
	gcc Ala															445	ō
	cac His															493	3
	gtg Val															542	1
	ctg Leu 160															589	Э
	tgc Cys															63*	7
	gtg Val															685	ō
	ccc Pro															733	3
	ccc Pro															78:	1
	cac His 240															829	9
aat	gtg	ggc	tac	cac	gtg	gag	cac	cac	gac	ttc	ccc	agc	atc	ccg	ggc	87	7

Asn Val Gly Tyr His Val Glu His His Asp Phe Pro Ser Ile Pro Gly 255 260 265 270	
tac aac ctg ccg ctg gtg cgg aag atc gcg ccc gag tac tac gac cac Tyr Asn Leu Pro Leu Val Arg Lys Ile Ala Pro Glu Tyr Tyr Asp His 275 280 285	925
ctg ccg cag cac cac tcc tgg gtg aag gtg ctc tgg gat ttt gtg ttt Leu Pro Gln His His Ser Trp Val Lys Val Leu Trp Asp Phe Val Phe 290 295 300	973
gag gac tcc ctg ggg ccc tat gcc agg gtg aag cgg gtg tac agg ctg Glu Asp Ser Leu Gly Pro Tyr Ala Arg Val Lys Arg Val Tyr Arg Leu 305 310 315	1021
gca aaa gat ggt ctg tga geeegg getgeeteet ggtggtggee attgteeece Ala Lys Asp Gly Leu * 320	1075
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actgctgccc ttgtccccga ggagtgtccc gcgcagccac acctggcaac agcagtgtgg	1195
gctgcagggc tccgtctgca cgtggacttg ccctggacct tgagtgtggc cctccctttc	1255
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As						cct Pro 80		-	-			_	_	_			291
	~	•		-		cag Gln		_		_		_					339
			_	_	-	tac Tyr						_		_	_	_	387
				_		gca Ala	-	_						_			435
_	.u S	-	_		_	cgc Arg		-				_	_				483
-	ıl V	_		_		aac Asn 160			_	-			-				531
						gac Asp									_		579
_					_	tgc Cys	-	_	-				-			_	627
		er				gga Gly											675
	ılL					ttg Leu											723
	l L	-	_	-	_	gcc Ala 240				_		-		-	-	-	771
						gac Asp											819
						ctg Leu											867

			270				275					280		
					acc Thr									915
	-		-	-	ttc Phe		_		_	_	-	-	_	 963
	_	-			atc Ile 320			_	-					1011
					gag Glu									1059
					ttg Leu									1107
					gga Gly									1155
					gag Glu									1203
					aac Asn 400									1251
					atc Ile									1299
					cac His									1347
					cat His									1395
					tct Ser									1443
					gcc Ala 480									1491
					tgg Trp									1539

			-		tca Ser	-	-	-	_	-	_	_			_	1587
_	-		_	-	agc Ser											1635
		_			aac Asn	_					_				_	1683
			_	_	gtc Val 560	-	-		-	-						1731
-	-		-	-	gag Glu		-					_	-			1779
					atc Ile			-	_	~		~ ~	~ ~		~ ~	1827
					caa Gln											1875
					gtt Val											1923
_	_		_		ttc Phe 640		_	_					_	_		1971
	_			_	gag Glu								_		_	2019
					cgc Arg											2067
		-	_		gaa Glu				_		_					2115
	-		-		ttg Leu				_							2163
_	_	_			gga Gly 720		_						_	_		2211

	tct Ser	_				-	_		_	-				-	2259
	ttg Leu														2307
-	gaa Glu				_	_	_		-	_	-	_	_		2355
	att Ile 780						_		~	~	~ ~		-		2403
	tca Ser														2451
	cag Gln														2499
	ttc Phe					-	-	_	_		_				2547
_	tac Tyr	_	_		~		_	_				~		_	2595
	gta Val 860														2643
	gat Asp												taa *	aaa	2691
aaat	tttt	ag c	catac	atta	a aç	ıtttc	tctt	tta	ıaaaa	l					2728

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<211> 1265
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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (546)..(857)

<400> 183

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<210> 184

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		tcc Ser	_		-	_	_			-			_	-		721
		tgg Trp 160						_	_			_		_	_	769
		agg Arg														817
		tcc Ser	-		-	_					-				_	865
		gtc Val														913
	_	tct Ser				_			_					_		961
	_	tgg Trp 240					_					_			-	1009
		ggt Gly							-	_	_				_	1057
-		gtc Val				-				_						1105
_		ttc Phe	_					_				_			_	1153
		ttc Phe														1201
		aca Thr 320		-			-			-		-		tga *	ggc	1249
ctgt	gctg	ga g	gtaco	gtaga	ac ca	gtgt	cgto	gtg	gaggg	gtg						1288

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<211> 3956 <212> DNA

<213> Homo sapiens <220>

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<400> 185

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	-		_		cag Gln	_	_	_		_				_	_	1	172
	_	_			ggg Gly		_	-			_		_		_	1:	220
_	-	-			att Ile	_			_		_	_	_		_	1:	268
-	_	_	_	_	cag Gln 150		_	_	_	-		_			_	1	316
					tat Tyr					_	_	_		_		1.	364
					cag Gln											1	412
					acc Thr											1.	460
					tcc Ser											1!	508
	_				tac Tyr 230	_	_	_		_		_		_	_	1!	556
_		_	-	_	ctg Leu	_				_	_	_	_	_	_	10	604
					cat His		-	_				_			_	10	652
	_			-	tca Ser	-	_			-	-	-				1	700
					tcc Ser		-							_		17	748
	-		-	-	ctg Leu 310			-	-	_			_	_		17	796

	cct Pro	-		_	-	_							_			1	844
	aaa Lys															1	892
_	tcc Ser		_	_	_			_		_		-	_			1	940
	atg Met 370															1	988
	atc Ile			-		_	_	-				_				2	036
	aag Lys			_		_		_					_	~		2	084
	ttc Phe		-	_	-					_			_	~		2	132
	tcg Ser		-		_		_	-	_	_	_		_	_	_	2:	180
	ggg Gly 450	-		-		_	-					_				2:	228
-	ccc Pro			_	_	_	_		_	_		-				2	276
-	aat Asn	-									_		_	-	_	23	324
	ctg Leu	_		_	_						-	_	_	-		23	372
	agc Ser		-		_			_	_							24	420
	act Thr 530	_	-	_	_		-					_	_			24	468
gca	gaa	atc	cct	gaa	ctc	caa	gat	atc	tct	gcc	ctg	gcc	cag	gac	aca	25	516

Ala 545	Glu	Ile	Pro	Glu	Leu 550	Gln	Asp	Ile	Ser	Ala 555	Leu	Ala	Gln	Asp	Thr 560	
	-	-		-	-		_	ccc Pro			-		-			2564
_		_		-				ctt Leu 585	_		-	_	_		_	2612
								tct Ser								2660
		_			_		_	gtt Val	-	-	-	_	_		_	2708
	_		_				-	cat His			-					2756
_		_	-	_				cta Leu	-			_				2804
					_		_	ttt Phe 665			_	_	_	_		2852
								gtg Val								2900
_		-		_				cac His			-	-	-	-		2948
		-	-			_	_	gaa Glu	_	_					-	2996
			_	_	_	-	_	agg Arg					-	-		3044
_			-	_		_		cca Pro 745			_		_	_	-	3092
								gcc Ala		-						3140
								ggg Gly								3188

770 775 780	
act ccc ttt ctt ccc cag gtg ttc agc tcc cga cag gca ctg aat ggc Thr Pro Phe Leu Pro Gln Val Phe Ser Ser Arg Gln Ala Leu Asn Gly 785 790 795 800	3236
cat gcc cgc atc cac ggg ggc acc aac cag gtg acc aag gcc cga ggt His Ala Arg Ile His Gly Gly Thr Asn Gln Val Thr Lys Ala Arg Gly 805 810 815	3284
gcc atc ccc tct ggg aag cag aag cct ggt ggc acc cag agt ggg tac Ala Ile Pro Ser Gly Lys Gln Lys Pro Gly Gly Thr Gln Ser Gly Tyr 820 825 830	3332
tgt tcg gta aag agc tca ccc tct cac agc acc acc agc ggc gag aca Cys Ser Val Lys Ser Ser Pro Ser His Ser Thr Thr Ser Gly Glu Thr 835 840 845	3380
gac ccc acc acc atc ttc ccc tgc aag gag tgt ggc aaa gtc ttc ttc Asp Pro Thr Thr Ile Phe Pro Cys Lys Glu Cys Gly Lys Val Phe Phe 850 855 860	3428
aag atc aaa agc cga aat gca cac atg aaa act cac atg cag cag gag Lys Ile Lys Ser Arg Asn Ala His Met Lys Thr His Met Gln Gln Glu 865 870 875 880	3476
gaa caa cag agg caa aag gct cag aag gcg gct ttt gca gct gag atg Glu Gln Gln Arg Gln Lys Ala Gln Lys Ala Ala Phe Ala Ala Glu Met 885 890 895	3524
gca gcc acg att gag agg act acg ggg ccc gtg ggg gcg ccg ggg ctg Ala Ala Thr Ile Glu Arg Thr Thr Gly Pro Val Gly Ala Pro Gly Leu 900 905 910	3572
ctg ccc ctg gac cag ctg agt ctg atc aaa ccc atc aag gat gtg gac Leu Pro Leu Asp Gln Leu Ser Leu Ile Lys Pro Ile Lys Asp Val Asp 915 920 925	3620
atc ctc gac gac gtc gtc cag cag ttg gga ggt gtc atg gaa gag Ile Leu Asp Asp Asp Val Val Gln Gln Leu Gly Gly Val Met Glu Glu 930 935 940	3668
gct gaa gtt gtg gac acc gat ctt ctc ttg gat gat caa gat tca gtc Ala Glu Val Val Asp Thr Asp Leu Leu Leu Asp Asp Gln Asp Ser Val 945 950 955 960	3716
ttg ctt cag ggt gac gca gaa cta taa agccc tgtgtgtcac ttagagacag Leu Leu Gln Gly Asp Ala Glu Leu * 965	3768
tgaaaaccca cggcctccat cttcattaat caggaaacct ggactgcctg cttgttttgt	3828
aaccctttta aactacctgt tttaaaagtg gtcattttat tcaggtttag aaaaaaaaat	3888
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                                                                      120
aggaagaaga cgcagaagca ggacgaccct gaaagattca gcctcttcat cctcaaacag
                                                                      180
gtcgcttctc gggagttctt ggtgttggaa tattttacag caaagcagtc gaccaggcct
                                                                      240
cctcttccca cctgtccagc agcatgaaag cagcatgatt ggccgaccgc aggagaagcc
                                                                      300
cccagaacca ggcccccaac tcagccatct gcggaggtca aggtgtgagc gacgtctcct
                                                                      360
caccacagtg ctgtgtggtc tatacctcag ccagggagag gatgtgaaac ccccgccct
                                                                      420
gcacatgagt ggtacaggcc aacaggaaca cctggctcca gccacgttca cagacatgtc
                                                                      480
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                                                                      540
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                                                                      660
taccaacage caccacttgg cgtccacage gggetgagee cactgatgge taccaataca
                                                                      720
cctactccca ggccagcgag atccggaccc agaagcttac cagcggtgtc ttacacaagc
                                                                      780
                                                                      836
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                                                                      884
atg gcc cag gtg ctg cac act cag tca gca gtg atg gat gga gcc cct
Met Ala Gln Val Leu His Thr Gln Ser Ala Val Met Asp Gly Ala Pro
                                     10
                                                                      932
gac agt get etc ege eag etg etg tet eag aag eec atg gag eec eea
Asp Ser Ala Leu Arg Gln Leu Leu Ser Gln Lys Pro Met Glu Pro Pro
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gca ccg gct atc cct tcc cgc tac cag cag gtg ccc cag cag cct cac
                                                                      980
Ala Pro Ala Ile Pro Ser Arg Tyr Gln Gln Val Pro Gln Gln Pro His
         35
                             40
cct ggt ttc act ggt ggg ctg tcc aaa cca gct ctt cag gtc ggg cag
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Pro Gly Phe Thr Gly Gly Leu Ser Lys Pro Ala Leu Gln Val Gly Gln
     50
                         55
                                             60
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						ctg Leu			-		_	_		_	_	1076
						gga Gly										1124
	_		_		_	atg Met	_	_		_				_	_	1172
	_	_		-		caa Gln	_	_			_		_		_	1220
_	_	_				cgc Arg 135			_		-	_	_		_	1268
_	_	-	_	_	_	cta Leu	_	_	_	_		_			_	1316
_			_			cag Gln				_	_	_		_		1364
						atg Met		-								1412
						cca Pro										1460
	_			_		cag Gln 215				_			_	_		1508
	-					cag Gln	_	_		_		_		_	_	1556
-		_	_	_	_	aag Lys				-	-	-	-	-	-	1604
-	_	_	_			ggg Gly	-	_				-			_	1652
	_			_		gat Asp	_			_	_	_				1700
cat	cgc	CCC	ctc	cta	tcc	ccc	agt	ggg	atc	cac	ctc	aac	aac	atg	ggg	1748

His	Arg 290	Pro	Leu	Leu	Ser	Pro 295	Ser	Gly	Ile	His	Leu 300	Asn	Asn	Met	Gly	
	_		_	_	ctg Leu 310			-	_	_			-			1796
		_		-	gcc Ala	_							-			1844
					GJÀ âââ											1892
_			_	_	aag Lys			_		_		-	_			1940
					Gly ggg											1988
_					cat His 390											2036
	-			_	gag Glu	_		_					_	-		2084
			_	_	ccg Pro					_			_	_		2132
	_		_		ctg Leu		_	_	_	_	_		_	_	_	2180
					ctc Leu											2228
_				_	ctg Leu 470	_	_	-	-	_		_				2276
_		_			tcc Ser			-		~ ~	-		_	_	_	2324
	_	_		_	acg Thr						_	-	_	_		2372
					agc Ser											2420

			515					520					525				
									atc Ile								2468
	-	-			-			-	atc Ile		-	_	-	-	-		2516
		_	-		-	_		-	ccc Pro			_		_			2564
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	_	-							tct Ser	-		-	_			_	2660
									gtt Val								2708
		_		_				_	cat His			_					2756
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	_		_			_		-	ttt Phe 665			-	-	-	-		2852
	_		_	_		_	_	_	gtg Val					_			2900
	_		_		_				cac His			-	-	-	-		2948
									gaa Glu								2996
				-	-	-	-	-	agg Arg					-	_		3044
٠	_			_	_		_		cca Pro			-				-	3092

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		Cys Gly Ala V	tg ttc agc tcc cga cag al Phe Ser Ser Arg Gln 780	3188
		Ile His Gly G	gc acc aac cag gtg acc ly Thr Asn Gln Val Thr 95 800	3236
			ag aag cct ggt ggc acc ln Lys Pro Gly Gly Thr 815	3284
	r Cys Ser Val		cc tct cac agc acc acc co Ser His Ser Thr Thr 830	3332
	-		cc tgc aag gag tgt ggc co Cys Lys Glu Cys Gly 845	3380
•	_	Ser Arg Asn A	ca cac atg aaa act cac la His Met Lys Thr His 860	3428
		Arg Gln Lys A	ct cag aag gcg gct ttt La Gln Lys Ala Ala Phe 75 880	3476
			et acg ggg ccc gtg ggg nr Thr Gly Pro Val Gly 895	3524
	ı Leu Pro Leu		gt ctg atc aaa ccc atc er Leu Ile Lys Pro Ile 910	3572
			cc cag cag ttg gga ggt al Gln Gln Leu Gly Gly 925	3620
			at ctt ctc ttg gat gat sp Leu Leu Leu Asp Asp 940	3668
caa gat tca gt Gln Asp Ser Va 945		Gly Asp Ala G	aa cta taa agccctgtgt Lu Leu * 55	3717
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gcctgcttgt ttt	gtaaccc tttta	aacta cctgtttta	aa aagtggtcat tttattcagg	3837

3897 tttagaaaaa aaaatcctat ttcttttcct tttatttaaa aaaatttgtt tttgtggggg gttgggggaa taaataattg gcacaactat ctttaagagg tgtttcatct gggctacctt 3957 4017 ctcatgaaat cattcccagt agggactgaa gctgaccttc atgttccatt gcattcagat 4077 gtcaaccatc ccggttgcct tttatcccaa agcttgctgt gagtgtgtgt gtgtgagacg caggegacce tettagtact ggggtettgg ggecaacttt teecateaag egttactttg 4137 attctgttct gacctcattc catagtttgc agtgagcatg gcatctttgc ctggagatac 4197 tatgctaggg ccagctttcc aggggcaaag caagccctcg tgttacacgg ctctcctcca 4257 4317 gctcacacga catgtgagga gatgaccaaa tgtgaaaaca ggtttcccct gtgttgcccg tcatcctttg gcccgttcac aggaatggag tactgtataa ttttaggctt tcattcccag 4377 cagtgtttac tgaggacctg gttttctaga acaggtgtgt cctgtcctct tccatgttcc 4437 ctgggggctg gtcagctcca agttgtgggt ggcagagctg tgtttcagca tgaactgact 4497 agagacccat ctggaggcaa atattaagtt gccaggactg ctttcacttc agggtgattg 4557 aaggacacat attgaagtac ctagaatgcc agaaagtgtt ctattgccca aac 4610

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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (367)..(1524)

<400> 187

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15					20					25					30	
					ggg Gly											504
					tgt Cys											552
			_		tat Tyr					-					_	600
_		_			ctt Leu			_	_		-	_		_		648
-	-	-			act Thr 100	_	_	_			_		-		_	696
					gaa Glu											744
_	_	_			aac Asn		_			-				_		792
					att Ile											840
_		_			aaa Lys						-			-		888
					tat Tyr 180											936
					gat Asp											984
		_		_	ctc Leu						_	-	-			1032
		_			aaa Lys			_								1080
-	-		_		aac Asn					_	-					1128

tat gtc agg cga ctg gac ttc ttt gaa aaa cct gat tat gag tat tta Tyr Val Arg Arg Leu Asp Phe Phe Glu Lys Pro Asp Tyr Glu Tyr Leu 255 260 265 270	1176
cgg acc ctc ttc aca gac ctc ttt gaa aag aaa ggc tac acc ttt gac Arg Thr Leu Phe Thr Asp Leu Phe Glu Lys Lys Gly Tyr Thr Phe Asp 275 280 285	1224
tat gcc tat gat tgg gtt ggg aga cct att cct act cca gta ggg tca Tyr Ala Tyr Asp Trp Val Gly Arg Pro Ile Pro Thr Pro Val Gly Ser 290 295 300	1272
gtt cac gta gat tct ggt gca tct gca ata act cga gaa agc cac aca Val His Val Asp Ser Gly Ala Ser Ala Ile Thr Arg Glu Ser His Thr 305 310 315	1320
cat agg gat cgg cca tca caa cag cag cct ctt cga aat cag gtg gtt His Arg Asp Arg Pro Ser Gln Gln Gln Pro Leu Arg Asn Gln Val Val 320 325 330	1368
agc tca acc aat gga gag ctg aat gtt gat gat ccc acg gga gcc cac Ser Ser Thr Asn Gly Glu Leu Asn Val Asp Asp Pro Thr Gly Ala His 335 340 345 350	1416
tcc aat gca cca atc aca gct cat gcc gag gtg gag gta gtg gag gaa Ser Asn Ala Pro Ile Thr Ala His Ala Glu Val Glu Val Val Glu Glu 355 360 365	1464
gct aag tgc tgc tgt ttc ttt aag agg aaa agg aag aag act gct cag Ala Lys Cys Cys Cys Phe Phe Lys Arg Lys Arg Lys Thr Ala Gln 370 375 380	1512
cgc cac aag tga cca gtgcctccca ggagtcctca ggccctgggg actctgactc Arg His Lys * 385	1567
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<213> Homo sapiens

<220>

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75	80		85	
-		-	c gat cac tgc atg o Asp His Cys Met)	
			t gtg tct gtt ctg y Val Ser Val Leu 120	
			a cca acg ttc aga n Pro Thr Phe Arg 135	
• •	Ile Arg Asp I		a gac aat ctc ttt n Asp Asn Leu Phe 150	
			g gag act gtg cac 1 Glu Thr Val His 165	
			g caa att gag aaa s Gln Ile Glu Lys)	
			c cat gtt ggc ccc e His Val Gly Pro 200	
cag atg cac tga Gln Met His * 205	ata ttttgtctt	tg ttgcaagtca a	attaggtgtc ttgtgaa	acaa 1162
ggaaatacta atcto	ctaagc tgcctg	ggtc tttttgtgtç	g aatatttaat ggtgo	ctccat 1222
gactgttgag tttta	aaaac ctcgtta	aaat tttgccaaat	cagttgcccc caaa	agggaa 1282
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		_		c ctg agc cac p Leu Ser His 10		167
gcc atg atc to Ala Met Ile Le 15					5 5	215
ggc atc tct gg Gly Ile Ser Gl		•		-		263
agg tac ctg ga Arg Tyr Leu As			e Ile Ser			311
atg aag gtg gt Met Lys Val Va 65					9	359
tat ggg aaa tt Tyr Gly Lys Ph 80	_	_			 -	407
ctg gag ttt ct Leu Glu Phe Le 95		_			-	455
tac agt ttc ac Tyr Ser Phe Th						503
gaa tca gtg gc Glu Ser Val Al 13	a Ile Leu		ı Phe Met			551
gag gct gag ac Glu Ala Glu Th 145						599
cgg gca ctc ta Arg Ala Leu Ty 160	r Leu Ala .				55	647
ttc tat gac ca Phe Tyr Asp Gl 175						695
tac tgt gac tt Tyr Cys Asp Ph					22 2	743
aag tta agt ct Lys Leu Ser Le 21	eu Pro Met	-		tcagagaca gto	ctacgcct	795
taacaagcac atg	gaaggaaa ct	attctgaa tg	gttctcttt	ggcaacttat d	ccataatttg	855

915 ggatcaaatg ttaaaaccag aaaagtgttt agtgtggatt tcagcaaaac ctgatcatcc 975 cacccagaag accttctcat caatagatcg cccttaaaga cccattgtaa ggtcataaaa aacctcggcc aactgcacaa agatggtgcc tcactgcaac aagaaacctt aaggtgtctt 1035 1095 accgacgaaa taaaaaacat aaatgattgt tctccaaggc ctgagggcaa gactcatgat gagcaagtca accccaatct ggaacaatgt ccctcctctt agaatgtccc aactaaagac 1155 1215 cagttaaaat attagggtac gttcttgtga atttccactt tccaggtaga tgaccaaatt 1275 taggtggtca agatataaag gtgtcagcta gttttaagtg tgaaacttat ttcactttca 1335 cactgccttc aggccagaag caaaccaaat ttaccaggtt tggctggagg agttttgtga 1395 ctcatctttt actggtttga attttttcaa accagtggct gatacctgcc ttgtacttag taccttaata ccaataacct aatggtactt aggcgagtac catttgcaca atcactgttt 1455 tacttatgag cagatacaga tatatccaaa cccttaccta ctaggtatcc tgctagggtt 1515 ttcaattcca attcttgtat taagtttttt cctttcagtt ttaggtgcga aagtaatcag 1575 tcaatccaat atcccccatc tttgtcttga aacaaaaact gttttaagac gtctacgttg 1635 aattattcag agaattaagc aataaaagct cacaccttat tgtcaaaaaa 1685

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<211> 716

<212> DNA

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<220>

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	_		_			acc Thr			_	_	_				_	315
						gta Val										363
						atc Ile										411
						ata Ile										459
						ctg Leu 110										507
						att Ile										555
						ttc Phe										603
						cca Pro				tga *	ggad	cctt	c aga	agaca	agtc	654
taco	gcctt	caa o	caago	cacat	cg aa	aggaa	aacta	a ttt	tgaa	atgt	tcto	ctttg	ggc a	actt	tatcca	714
ta																716

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caaa	gtga	ctg g	gttt	tgcag	ga to	gggag	gccad	c cat	gcco	cagc	ctag	gtcto	cac t	ttat	taggct	300
ccca	.aacc	cac a	agcag	gaaca	ac ct	zggct	zgact	cat	ccct	ctg	caco	ccato	cac g	gccag	gtgggc	360
atgc	tggc	ctg t	taggt	-gggg	Met				a Arg						c tgg r Trp)	412
tgt Cys																460
gtt Val																508
gct Ala																556
tgg Trp:																604
att Ile						-										652
ggc Gly																700
gcc Ala	tag *	acco	cctgg	gga g	ggcct	ccaa	ag to	ccta	aggt	: tag	gacat	ctc	ctg	gggtg	gct	756
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tgac	ctgo	cag g	ggago	ctgga	aa to	gctgt	ggga	a ggg	rccct	gac	cccg	gggg	ccc a	atgga	agctcc	876
ctag	gcto	cct o	ctggd	ccaca	ac gg	gacgo	gtgg	ggto	gaco	cgg	gaat	tccg	ggg d	ccggt	accga	936
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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (47)..(943)

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gta cag gtg ctt Val Gln Val Leu 20					151
cag gct ccg aac Gln Ala Pro Asr			Gln Pro Gln		199
agc caa atg tcg Ser Gln Met Ser 55	Leu Pro Ala				247
gtg gag cag cca Val Glu Gln Pro 70					295
ttt gag ggg cgc Phe Glu Gly Arg 85		Thr Val Thr			343
tct gtg cct aag Ser Val Pro Lys 100					391
gcc tct gag aag Ala Ser Glu Lys			Leu Lys Met		439
gaa gct cag att Glu Ala Gln Ile 135	Asp Thr Asr		Met Ile Val		487
aag aag gct ctt Lys Lys Ala Leu 150					535
ccc tcc acc cac Pro Ser Thr His 165		. Ala Gly Met			583
caa cag aaa tgt Gln Gln Lys Cys 180					631
tcc cta acg aca Ser Leu Thr Thi			Ala Val Pro		679

cag ttc atg cgt att cag aat gta ggc caa aag aaa gct gaa gag agt Gln Phe Met Arg Ile Gln Asn Val Gly Gln Lys Lys Ala Glu Glu Ser 215 220 225	727
cca gca gaa att atc atc cag gct att cct cag tat gct att cct tgt Pro Ala Glu Ile Ile Gln Ala Ile Pro Gln Tyr Ala Ile Pro Cys 230 235 240	775
cac tcc agc tcc aat gtg gtg gtg gag ccc agt ggg ctt ctt gag cta His Ser Ser Ser Asn Val Val Val Glu Pro Ser Gly Leu Leu Glu Leu 245 250 255	823
aac aac ttc act agt caa cag ctg gat gat gag gag aca gca atg gagAsn Asn Phe Thr Ser Gln Gln Leu Asp Asp Glu Glu Thr Ala Met Glu260265270275	871
cag gac ata gac agt agc acg gag gat gga act gaa ccc agc cct tct Gln Asp Ile Asp Ser Ser Thr Glu Asp Gly Thr Glu Pro Ser Pro Ser 280 285 290	919
cag agc tct gct gaa cgg tcc tag tgtttggaca caatagtgca ctttaaaacc Gln Ser Ser Ala Glu Arg Ser * 295	973
tgcttggtta ccaagtgtcc agggaaaccc ttgtattttg atgactaaaa agagcacttt	1033
gcccgtactt aggctgtgga ccctaaaaca gcagtgtttc aacaagatgt tgctgcagga	1093
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aaaaagaaaa gaac atg gag gca gat ata atc aca aat ctt cga tgc agg Met Glu Ala Asp Ile Ile Thr Asn Leu Arg Cys Arg 1 5 10	230
ctc aaa gag gct gaa gaa gag cga cta aaa gct gca cag tat ggt tta Leu Lys Glu Ala Glu Glu Glu Arg Leu Lys Ala Ala Gln Tyr Gly Leu 15 20 25	278

						aat Asn 35										326
_		_	_	_		atg Met			-							374
						gaa Glu										422
						att Ile										470
	-	_	_			agc Ser	_	_			_	-	-			518
						aaa Lys 115										566
	_	-	-	_	_	aag Lys			_	_						614
						gaa Glu										662
						atg Met										710
_		_	_	_		acc Thr			_	_			_			758
	_		_	_		gaa Glu 195										806
~	_					gaa Glu		-		_			_	-		854
				_		gag Glu		-	-	_	_					902
						gca Ala										950
aaa	ggc	aac	tct	ttg	ttt	gca	gag	gtg	gaa	gat	cga	agg	gca	gca	atg	998

Lys Gly Asn Ser Leu Phe Ala Glu Val Glu Asp Arg Arg Ala Ala Met 255 260 265	
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caa aat gta ttt aac aga gaa cag atg cag aga atg aag tta caa att Gln Asn Val Phe Asn Arg Glu Gln Met Gln Arg Met Lys Leu Gln Ile 285 290 295 300	1094
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ctt tta ggt gaa att aga aat ctg gag aaa ttt aag aat tta tat gac Leu Leu Gly Glu Ile Arg Asn Leu Glu Lys Phe Lys Asn Leu Tyr Asp 335 340 345	1238
agt atg gaa tcc aag cct tca gtc gac tct ggt act ctg gaa gat aac Ser Met Glu Ser Lys Pro Ser Val Asp Ser Gly Thr Leu Glu Asp Asn 350 355 360	1286
acc tat tat aca gat tta ctt cag atg aag ctg gat aac tta aac aaa Thr Tyr Tyr Thr Asp Leu Leu Gln Met Lys Leu Asp Asn Leu Asn Lys 365 370 375 380	1334
gaa att gaa agc act aaa ggt gaa ttg tcc ata cag cga atg aaa gca Glu Ile Glu Ser Thr Lys Gly Glu Leu Ser Ile Gln Arg Met Lys Ala 385 390 395	1382
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tagatgaatt gaaactaaaa tatgaacctg aagagacagt tgaagtgcct gtactgaaaa	1546
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acaccccaaa ctctcccagg ttagctgctg aatcaaagct tcaaacagaa gttaaagaag	1906

1966 gaaaagaaac ttcaagcaaa ttggaaaaaag aaacttgtaa gaaatcacac cctattctat atgtgtcttc taaatctact ccagagaccc agtgccctca acagtaaaga cttttcttta 2026 agtaagagta cggtgccact tgcctcaaaa gttactatgg tgcttaagat tgtcttgatc 2086 tgacatatat caccttctgg gttatttact cattgtgcca ggacctggca ttttcatgtg 2146 2206 cctttgacca agtgttcaga atttgcttga ctctaacctg gagagcttct taagtgatgc cccttcatgg agcttctatg acagtgaata aactattaat tgaaggaaaa tgttataatt 2266 aatgtatcta tttgctgcat tgtatatgga ttaaatgata aaaaacaagt aatctaccct 2326 cagagecatg tatttgagaa tgetteaate atatttteet atgtaetttt ttttataaae 2386 2446 ttagttttag actatgttgt aaaaatggga aggttgtaaa ctatgttgta aaaataggaa atgtggctta aaatatatac attatattgt ttcaggattt tgtcagtgtt taaagaacca 2506 tgttcatctt tgtatttata tacatgattt aaattttgtc taaaatttta aataaaactg 2566 ccagtgattt atcctt 2582

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1

			_	_	aag Lys		_					_		-		584
			_		cca Pro 25	_	_			_						632
-	-	~ ~			ggc Gly	_	•	~	~ ~		_			_	_	680
					tgt Cys											728
				-	gtc Val			_	-							776
					gtg Val											824
_			_		cat His 105		~ ~	_	_	-			-			872
					gcc Ala											920
					ttc Phe					tga *	gcts	gaato	g tto	etggg	gcag	971
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ctca	ataa	at g	I													1042

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1 5 10

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	ggc Gly															145
	gcc Ala 45															193
_	cac His	_							_			-	_			241
	Gly gag															289
-	g gga n Gly				-			_		_			-			337
	tct Ser								_		-		-		_	385
	aat Asn 125															433
	gag Glu					-			-	_	_	_			-	481
	gat Asp		_	_	_			-								529
	atc lle			_		_					-		_			577
_	gct Ala	_														625
	tcg Ser 205		-	-	-		_							_		673
	tat Tyr															721
aaç	g aag	cca	aga	tgc	taa	gcta	ag g	gtgad	ctata	ag ca	accct	ggct	gtt	ttct	tct	775

Lys Lys Pro Arg Cys ^ 240	
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att cta gct aac cgc gtc ggg gag cgg cgc cgg gag aag ggc gag gcg Ile Leu Ala Asn Arg Val Gly Glu Arg Arg Arg Glu Lys Gly Glu Ala 30 35 40	147
act tgc atc acg gag atg tcg gtg atg atg gct tgc tgg aag cag aat Thr Cys Ile Thr Glu Met Ser Val Met Met Ala Cys Trp Lys Gln Asn 45 50 55	195
gaa ttc cgc gac gat gcg tgc aga aaa gag atc cag ggc ttc ctc gat Glu Phe Arg Asp Asp Ala Cys Arg Lys Glu Ile Gln Gly Phe Leu Asp 60 65 70 75	243
tgt gcc gcg agg gct cag gtg acc gat ggc tcc tgg ggt gct ttc tca Cys Ala Ala Arg Ala Gln Val Thr Asp Gly Ser Trp Gly Ala Phe Ser 80 85 90	291
gga aaa gaa tgg ggg aga tag aa gtaatgattc tccctgcctt ttgctaggaa Gly Lys Glu Trp Gly Arg * 95	344
aggccctttc attcatttgg gaggtatatt attcacgcca aagtgggaaa ggttacagtt	404
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524

584

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aatgggaaaa tcattttgaa aaatgtaaat tgctgctcaa gtagacatta ttgtgtgaaa

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	ga cag tcc c ly Gln Ser G 10					
Phe Val M	tg ggt tgc g et Gly Cys A 25			Ala Glu A		
	cc tgt ctc a er Cys Leu A					
	gg aaa acc a ly Lys Thr M					
	tt ggg atg g le Gly Met G 75			c catggtt	gcc aactaca	1tct 296
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gagggttagg gtctctgcct gggat atg caa gag gaa gta gga aag ggt Met Gln Glu Glu Val Gly Lys Gly Gly 1 5	232
ctc atg gat gat cct agg ctg cta gaa gtc ctt aag gcc cca tct agt Leu Met Asp Asp Pro Arg Leu Leu Glu Val Leu Lys Ala Pro Ser Ser 10 15 20 25	280
cca ttc cac tcc cta ccc cca ttc cag agc cga gta gta agt tta cag Pro Phe His Ser Leu Pro Pro Phe Gln Ser Arg Val Val Ser Leu Gln 30 35 40	328
atg ttt ccc cca tta cgt acc ccc acc cat ccc tgc tgc agc gag cct Met Phe Pro Pro Leu Arg Thr Pro Thr His Pro Cys Cys Ser Glu Pro 45 50 55	376
gag agc cag gca gag cca ggc aca gct cct cag tct tct cac aca gtc Glu Ser Gln Ala Glu Pro Gly Thr Ala Pro Gln Ser Ser His Thr Val 60 65 70	424
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cccgacagca gtggggtcca cacactgagc tccagctggc actgcccact caagggctga	815
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	g gaa gcc at Glu Ala Il 1							343
	agg gag co Arg Glu Pr 25							391
cac agc tgt His Ser Cys	ctc tct gg Leu Ser Gl 40	a ctc tgg y Leu Trp	gag atc Glu Ile 45	cca gga Pro Gly	gaa tcc Glu Ser 50	cag Gln	aac Asn	439
	acc tgt cc Thr Cys Pr							487
	aat tgg ca Asn Trp Gl							535
cta agg cta Leu Arg Leu 85	cat cca gg His Pro Gl 9	a atg ggg y Met Gly 0	ctg aag Leu Lys	ggt gac Gly Asp 95	ctg tgt Leu Cys	Glu :	cgc Arg 100	583

cat ggg gaa aag ctg aag atg ttc tgc aaa gag gat gtc ttg ata atg 631

His	Gly	Glu	Lys	Leu 105		Met	Phe	Cys	Lys 110	Glu	Asp	Val	Leu	Ile 115	Met	
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															gcc Ala	727
											tgg Trp 160					775
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											cag Gln					871
											gag Glu					919
											atg Met					967
											gtc Val 240					1015
											gtc Val					1063
											tct Ser					1111
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											gac Asp					1303

325					330					335					340	
			tat Tyr							_	_					1351
			tgg Trp 360													1399
			aag Lys													1447
			gga Gly													1495
			acc Thr													1543
			gga Gly													1591
			act Thr 440													1639
			ggg Gly													1687
			aac Asn													1735
gac Asp 485	taa *	gaaa	igct <i>a</i>	icc a	accct	aacc	a ca	ıgagg	gette	gaa	ittgg	igcc	tggd	cccc	at	1791
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Trp Asp Asn Ser Glu Ala Glu Glu Glu Glu Lys Ala Pro Val Leu Pro
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30

35

399

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gag agt aca gaa ggg cgg gag ctg acc cag ggc ccg gca gag tcc tcc 495 Glu Ser Thr Glu Gly Arg Glu Leu Thr Gln Gly Pro Ala Glu Ser Ser 40 45 50 55

tct ctc tca ggc tgt ggg agc tgg cag ccc cgg aag ctg cca gtc ttc 543 Ser Leu Ser Gly Cys Gly Ser Trp Gln Pro Arg Lys Leu Pro Val Phe 60 65 70

aag tcc ctc cgg cac atg agg cag gtc ctg ggt gcc cct tct ttc cgc 591
Lys Ser Leu Arg His Met Arg Gln Val Leu Gly Ala Pro Ser Phe Arg
75 80 85

											gtg Val					639
											gta Val 115					687
											agc Ser					735
											ccg Pro					783
									_	-	atc Ile			_		831
											tgt Cys					879
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											att Ile					975
											cag Gln					1023
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ggto	tato	at g	acta	gtgo	t go	tgtg	aaca	tto	ctga	ıtcc	ggto	tctg	gac a	ıaaca	cgcct	1317
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cct ggc ctt gac tta ggg ctg cac tgt atc ctc agc aac ggc ctt gca Pro Gly Leu Asp Leu Gly Leu His Cys Ile Leu Ser Asn Gly Leu Ala 10 15 20	161												
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tac att gtt tat tgg ctc cca aag tcg gga ttg aag agt gaa aag atg Tyr Ile Val Tyr Trp Leu Pro Lys Ser Gly Leu Lys Ser Glu Lys Met 75 80 85	353												
cag gca atg aat cct tct gca cac tcc tcc ccc cac att cct gac act Gln Ala Met Asn Pro Ser Ala His Ser Ser Pro His Ile Pro Asp Thr 90 95 100	401												
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gga cag aaa ata tac ccc tca cat cat c Gly Gln Lys Ile Tyr Pro Ser His His . 15 20	
ata gct tca ttg aag tgt cag cac tca : Ile Ala Ser Leu Lys Cys Gln His Ser : 30 35	
agg aaa aat agc aac agt aca acg ggg a Arg Lys Asn Ser Asn Ser Thr Thr Gly a	
atg ggc ata ggg aat agc ggc tca aat g Met Gly Ile Gly Asn Ser Gly Ser Asn v 65 70	
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tgtctttgct taacctattc aaccagaaat gaat	ggaget egaetggaaa ggaacagtet 423
tcagatgggt taagattgaa gggtggactg gact	cctactg agcaccgtcc ttcaacaagg 483
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Met Pro
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act c Thr L																212
ggt g Gly G 35						_	_		-		-		_	_	_	260
ttt c Phe G																308
gaa a Glu L				-		-	_	_		_		_				356
gaa co Glu P	ro G															404
aag ga Lys G																452
gaa aa Glu A: 115											tga *	tcca	a taa	aacca	agaa	502
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		20>														
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ggct	cata	agt 1	tg	_		-			_			-			c cca o Pro	228
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				tct Ser												276
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Ser	Val 30	Pro	Trp	Pro	Trp	Arg 35	Leu	Phe	Leu	Pro	Pro 40	Ala	Leu	Gly	Ala	
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																400
				ctg Leu												420
				65					70					75		
				aca Thr												468
501	110	110	80	1111	GIG	מעם	GTĀ	85	110	1 y 1	пси	- <u>y</u> -	90	1119	ASII	
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Glu	Asp	Asn 95	Ile	Asn	Asn	Asp	Gly 100	Arg	Lys	Thr	GLy	Leu 105	Gln	Gly	Leu	
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Trp				Gly											*	

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ser	Asp	ıyı	Asp	50	ьeu	GIU	Pro	GIU	55	ьeu	ASD	ser	vai	60	гур	
							gaa									301
ASII	GTĀ	GIU	65	Pile	ığı	ьeu	Glu	70	ser	GIU	Asp	GIU	75	GIU	ser	
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GIU	95	TIE	116	GIU	ASP	100	Tyr	пур	GIU	Arg	105	цур	тАт	GIU	PIO	
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Lys 110	пец	пур	GIII	r116	115	пЛя	Ile	шeu	ALG	120	пуз	ALU	TIGU	шеu	125	
_	-	-					agc		_				-			493
пλр	AT A	СУS	WOII	ட்தத் 130	пур	MDII	Ser	Holl	135	UDII	дтλ	FIO	val	140	TT6	

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					ctc Leu										637
					agc Ser 195		_	-		_	_		-		685
					cat His										733
_		-	-		att Ile		-	_	_	_			_	_	781
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					ctg Leu										877
					aga Arg 275	_		_	-				_	_	925
					tgg Trp										973
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	_			_	gaa Glu		_	_						_	1069
					aaa Lys										1117
				_	gaa Glu 355		_				_		-		1165

						aaa Lys										1213
		-	_	-		att Ile		_		_	-	-	_			1261
						ata Ile										1309
						agt Ser 420										1357
						aac Asn										1405
						gcc Ala										1453
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						atg Met										1549
						gaa Glu 500										1597
	_				_	ggg Gly							9.0			1645
	-	_		-		aag Lys	_	_			_		_	_		1693
						ctg Leu										1741
_	_				_	gaa Glu				_				-		1789
		-		_		gaa Glu 580	-		_	-		_		~		1837
ttt	ttg	cta	gtt	gtt	ggc	ttg	aaa	cat	tat	atg	cta	tgt	gta	cta	tta	1885

Phe 590	Leu	Leu	Val	Val	Gly 595	Leu	Lys	His	Tyr	Met 600	Leu	Cys	Val	Leu	Leu 605	
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-	-			-	caa Gln	-						-		-		1981
_	_		-		gat Asp	-			-				_		_	2029
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	-		-	_	cct Pro	-			-	-	-				-	2221
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					ttg Leu											2413
					aac Asn											2461
					gtt Val											2509
					gag Glu											2557

	815					820					825					
					ttc Phe 835										-	2605
					gtg Val		-		_					_		2653
_			-		gca Ala	_								_		2701
					ttt Phe	_	_							-	-	2749
		-			gtt Val	_	_			-	-		_			2797
					caa Gln 915	-			_	_			_		_	2845
					gaa Glu											2893
ttg Leu	tag *	ctgt	gctt	tc t	tgat	gcgt	a ga	aaca	ıcgtç	g cat	ggag	ggat	caaa	acact	igt	2949
caga	aatto	gat g	gaaat	caat	a ca	ıcaaa	ıgaga	ı taa	agtt	tag	cttc	etttt	ta c	ctatt	caata	3009
ttga	acat	aa t	atto	ıttaa	aa ta	ıttga	gatg	, aaa	ıtgct	gtt	ggat	ttga	ata c	catta	aatct	3069
taat	gtaa	ıta t	tgta	agac	t tt	tgaç	gaata	tac	ttga	itta	aaat	gtga	aaa g	gaagg	gattg	3129
ttaa	ictta	ıtt g	rctat	tttg	ıg ta	tata	atgt	taa	ıttta	ttg	acta	ıgttt	ga a	ataa	tgtga	3189
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		Ser Asp Ser		t tcc tca gcg r Ser Ser Ala	
				c agt gtg cag p Ser Val Gln 60	
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		~ ~		g ttc agt gaa g Phe Ser Glu 90	
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-	_	act Thr	-				_	-	_		_			~ ~	829
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		cat His													925
		ctt Leu													973
		act Thr 305													1021
		tca Ser													1069
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		atg Met													1165
		tta Leu													1213
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		agg Arg													1309
		 tct Ser		_	_	_		-	_				_		1357
		cat His													1405

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					aag Lys											154	49
					gca Ala											159	97
					att Ile 515											164	45
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					gaa Glu											178	39
	_				atg Met		-									183	37
					ggg Gly 595											188	35
	_				ctt Leu											193	33
					tct Ser											198	31
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					cta Leu											201	77
aca	tgc	aga	aga	acg	ctt	ttt	ggt	gac	tat	tcc	tta	aag	aca	cgc	aag	212	25

Thr 670	Cys	Arg	Arg	Thr	Leu 675	Phe	Gly	Asp	Tyr	Ser 680	Leu	Lys	Thr	Arg	Lys 685		
	_			_	agt Ser	_				_							2173
	-	-	_		ttt Phe	_					_	-	_	_			2221
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-	-		-		gtg Val										_	:	2461
		-	_		agt Ser						_			_		;	2509
		_	-	-	ctt Leu			-	_	_			_		_	:	2557
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895	900		905	
·	t aaa ttg ttc ttt e Lys Leu Phe Phe 915		ttg tag ctgtgctttc Leu *	2846
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	~ ~	~ ~	-		_	_	_	_	_	_		-	-	gga Gly		539
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			-		_		_			-				aaa Lys 125		683
	_	-									_	_	-	aag Lys		731
	-				-			_	_	_				agg Arg	_	779
-						_	_	_				-	-	ccc Pro	_	827
														ggc Gly		875
_	-				-	_		-			_			gct Ala 205		923
				_		_								cca Pro		971
					_									cct Pro		1019
													_	ctg Leu		1067
	-	_	_	_			_							agg Arg		1115

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gag gaa ggg gcg tca ttt tcc tgt tcg cac aaa ggc acc aca ggg gct Glu Glu Gly Ala Ser Phe Ser Cys Ser His Lys Gly Thr Thr Gly Ala 290 295 300	1211
aac agt ggg cct gca atc tta gat ccc atc ctt gcc ttc ttc gag gga Asn Ser Gly Pro Ala Ile Leu Asp Pro Ile Leu Ala Phe Phe Glu Gly 305 310 315	1259
tct ctt ggg acc ctc ctg gtt tta act ggg agg ccc aga cca act cct Ser Leu Gly Thr Leu Leu Val Leu Thr Gly Arg Pro Arg Pro Thr Pro 320 325 330	1307
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gca gta ctt agt t Ala Val Leu Ser S 5	-			
caa gtg gat agt g Gln Val Asp Ser (20				
ggt cga aat act o				
aat gag aaa aaa a Asn Glu Lys Lys <i>E</i> 55				
agt gaa gca aat g Ser Glu Ala Asn (70	Glu Leu Arg As			
aaa tcc tcc cat o Lys Ser Ser His A 85				
aac cca gta cag a Asn Pro Val Gln I 100				
caa aga gat gag d Gln Arg Asp Glu (
aag gca ttg tta d Lys Ala Leu Leu I 135	-	-		
tat gaa gat gct g Tyr Glu Asp Ala (150	-	er Thr Gln Ser		
aaa gat aaa aga a Lys Asp Lys Arg I 165	•		-	
tca cta aaa gat t Ser Leu Lys Asp I 180		_	-	
gaa gtg gtt ctg a Glu Val Val Leu I 2				
gaa agg aaa gat g	gct gaa atc ca	ag aag ctg aaa	aat gta atc	act caa 968

Glu Arg Lys Asp Ala Glu Ile Gln Lys Leu Lys Asn Val Ile Thr Gln 215 220 225	
tgg gag gca aag tat aag gaa gta aag gca aga aat gca caa tta ttg Trp Glu Ala Lys Tyr Lys Glu Val Lys Ala Arg Asn Ala Gln Leu Leu 230 235 240	1016
aaa atg ctt cag gaa ggt gaa atg aaa gat aag gca gaa ata ctt ctg Lys Met Leu Gln Glu Gly Glu Met Lys Asp Lys Ala Glu Ile Leu Leu 245 250 255	1064
caa gtt gat gaa tca caa agt atc aag aat gag ctc act att cag gtg Gln Val Asp Glu Ser Gln Ser Ile Lys Asn Glu Leu Thr Ile Gln Val 260 265 270 275	1112
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acaaatacca gttcatacat tcttgttcca ataggagtt atg gga gga aaa att	174

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Met Gly Gly Lys Ile

222

1

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att aaa ago Ile Lys Ser 40	r Ile Ser											318
aac aag gto Asn Lys Vai			Lys 2									366
att atc tac Ile Ile Tyr 70						taa * 80	tgac	agat	CC	aatga	acc	417
ttagaatcca	gtagcata	tg cttag	gcatac	ttc	tcta	gca	gttt	gagg	ıtg (ctaat	tttag	477
gtatactttc	acctaaag	aa attc	cagct	CCC	ccaa	att	aggt	atct	ca (ggagg	gtgtag	537
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60

120

45

50

Pro Lys Ser Gln Val Phe Lys Pro Leu Glu Leu Leu Trp His Ser Leu

40

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_			-										ggc Gly	_		775
	_	-	_						_				cct Pro		_	823
													gat Asp			871
-	~ ~ ~	_	_	_	_	-	-	-	_	_	-	-	att Ile		_	919
	_				_	_	_			_			atg Met 145	_	_	967
													att Ile			1015
-	_			-	_	_			-		_		aga Arg			1063
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_	_				-		_				_		gat Asp 225		_	1207
-							-		_		_	_	gtt Val			1255
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	_				tct Ser											1735
			_		cct Pro				-							1783
					gtc Val 425											1831
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				aca tgc atc a Thr Cys Ile A 560	
				ctc aag gac a Leu Lys Asp A 575	
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1

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						gaa Glu										573
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						ttg Leu										813
						agg Arg										861
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		aag Lys								429
		tgc Cys								477
		gat Asp 85								525
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		ttt Phe 165								765
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aga ggt ggg agc tac cgc ctc atc aag cag cca agg agg cag gat aag Arg Gly Gly Ser Tyr Arg Leu Ile Lys Gln Pro Arg Arg Gln Asp Lys 115 120 125	384
gaa gcc cca aag agg gac tgg ggg gct gat gag gac ggg gag gtg tct Glu Ala Pro Lys Arg Asp Trp Gly Ala Asp Glu Asp Gly Glu Val Ser	432

	130					135					140					
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			_	_	ctg Leu											576
~	_	_			tgt Cys			_		-					_	624
~ ~		_		-	atc Ile		-					-		_		672
					gac Asp 230											720
_		_	_		gtg Val	-		_				_				768
					ggt Gly											816
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				_	gag Glu											912
					ccg Pro 310											960
					aag Lys											1008
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					ccc Pro											1104

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ctc Leu								1248
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gag Glu								1440
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ccc Pro 530								1632
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tgc Cys								1728
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Pro Pro Lys Pro Leu Glu Gly Ile Pro Glu Arg Glu Phe Phe Val Lys	276 324
Pro Pro Lys Pro Leu Glu Gly Ile Pro Glu Arg Glu Phe Phe Val Lys 15 20 25 30 tgg gca ggg ctg tcc tac tgg cat tgc tcc tgg gtg aag gag cta cag Trp Ala Gly Leu Ser Tyr Trp His Cys Ser Trp Val Lys Glu Leu Gln	

65 70 75

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_		_			_	_			_	_	-		tgg Trp 140		612
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				-	_	_		-	-			-	ccc Pro		708
_		_	-		-	_	_		-				gag Glu		756
_	_	_				-		_	_	_		-	aag Lys	_	804
~ ~			_						_		-		cag Gln 220	_	 852
													gac Asp		900
													atc Ile		948
													tac Tyr		996
													ttt Phe		1044
			_				_						aag Lys 300		1092

-	_	gtg Val 305									-					13	140
	_	Gly	_	_	_		_	_	_		_					13	188
		gtg Val	_										-	_	_	12	236
	_	ggc					_	-	_	-						12	284
-		aag Lys			_		_				-			_		13	332
_		gat Asp 385		_	_	_	_						_			13	380
		gag Glu														14	428
		ctg Leu														14	476
		atc Ile														15	524
		aag Lys	-	-			_		_	_	_	_				15	572
		cgg Arg 465														16	620
		aca Thr					-	_			_					16	668
	_	tcg Ser	-				_	-	-	_		_	_	-		15	716
		tac Tyr														17	764

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						gag Glu										2004
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						atg Met 725										2388
		_	-	-		tcc Ser					_	-	-			2436
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Lys	Lys	Lys	His	Gly 755	Ser	Thr	Pro	Pro	Gly 760	Asp	Asn	Lys	Asp	Val 765	Glu	
_	_	_					_	_					_	ctg Leu	-	2532
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														gag Glu		2628
-								_			_	-		gag Glu		2676
	-		-											gag Glu 845		2724
_	_		-	_	-	_		-		_		-	-	atc Ile	_	2772
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_				-		_		-						gag Glu	_	2868
	_		-		-			_	_		-	_		cga Arg	_	2916
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		_	_	-							_			aat Asn	_	3012
_	_		_	_		_		-		_	_			atg Met		3060
														cga Arg		3108
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-	cac His		Leu					Glu					Ser		3924
	atc Ile	Tyr					Arg					Trp			3972
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Pro	cgg Arg 1280		_		Leu		_			Lys					4068
	aac Asn			Glu					Phe					Phe	4116
	ctg Leu		Gln					Glu					Arg		4164
	ctg Leu	Asn					Pro					Met			4212
	cgc Arg					Glu					Ser				4260
Ser	aag Lys 1360				Ala			_		Āla		_	_	_	4308
	gtc Val			${\tt Gln}$					Leu					Ala	4356
	acc Thr		Leu			_	_	Ser	_			_	Val	-	 4404
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		tcg Ser														155
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		ata Ile 50	_			_	_					_		-	-	251
	acc	tcg	ttt													299
		Ser	Phe	Leu	Ile	70					75		_			
Leu gga	Thr 65 ttt	Ser tac Tyr	aaa	aga	ttt	70 gaa	tcc	tgg	aga	gtt	75 ctg	_	agc	_	tac	347

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3126

90

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		agt Ser 115			-								_		_	562
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		gtg Val														754
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		tta Leu														850
_		act Thr														898
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		atc Ile	_	_	_		-	-			_		_			994
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~ ~	_		•		gac Asp		_						_		-	1426
	_		_		gca Ala								-			1474
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<220>

<221> CDS

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Met Pro Leu Phe Pro Leu 1 5

														gag Glu	_	643
		-												ctg Leu		691
														ctt Leu		739
														Gly ggg		787
														agg Arg 85		835
														aga Arg		883
	_			ctc Leu						tga *	aaga	agcc	c ct	caaa	agca	934
gcct	ggg	cag (caggi	taacg	gt gg	gttt	ccct	gcg	ggcc	ccct	cct	cca	gct (gcata	agactc	994
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Met Val Val Gly Ala Phe Pro Met Ala Lys Leu Leu Tyr

1 5 10

ttg ggc atc cgg cag gtc agc aag ccg ctt gcc aac cgt att aag gag
Leu Gly Ile Arg Gln Val Ser Lys Pro Leu Ala Asn Arg Ile Lys Glu
15 20 25

gcc q Ala 2 30																204
gct (Ala (_														252
ggc				_	_		_	-	-					_	_	300
gag (Glu 1																348
ggc (396
cac a His 1 110																444
gtg g Val (492
gcg g Ala A																540
gag g		-	_	_		_										588
gtg (Val :						tag * 180	ga (gettg	gctgg	ga tç	ggaad	cctga	a att	ttgga	acat	641
ggcci	tato	ıta d	cctaa	acgt	gg co	cttct	tcc	c gca	accad	ccct	tgc	ctgcg	gct g	ggcc	cagtgg	701
aaaco	cacc	ag g	gatct	tgat	tg ca	actt	ggca	a ttt	ggtt	cacc	ccto	gctga	ata a	agago	cagcca	761
ttac	ctgc	ca c	ctggg	gacca	ag ca	aggto	gaago	c gtt	cgcaa	acat	agco	cccct	taa a	atcat	ccttc	821
acct	ccta	atc o	ccca	actco	ca aa	accag	ggac	g acc	ctgca	aagg	tcc	cagco	cag (cagga	acaccg	881
tggg	cact	ct g	ggcaa	aatga	aa aa	aaatg	ggaad	c ctg	ggtct	tga	gctg	gaato	caa 1	tgtgt	tattg	941
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cact	ggaa	aca d	cctt	cttc	et ti	tgto	caato	c ggd	cacaç	gacc	acto	gtaaq	gga a	aatgo	cagtgt	1061
gttg	cagt	gg d	ccttt	tctc	cc co	cctca	acct	cta	aaggt	cag	ctct	tagct	tga g	gcato	cagtgc	1121

1181 tctcttaagg aggaaaaaaa cggtgcggct gggagcggtg gctcacgcct gtaatcctag 1241 caccttggga ggccgaggcg ggcggatcac ttgaggtcag gagttccaga ccagcctggc 1267 caacatggtg aaactccgtc tttcta

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80

817 gca gga aga aac ctt ttc aga gag ttc ctc cga aca gaa tac agt gaa Ala Gly Arg Asn Leu Phe Arg Glu Phe Leu Arg Thr Glu Tyr Ser Glu 100 865 gag aac cta ctt ttc tgg ctt gct tgt gaa gac tta aag aag gag cag Glu Asn Leu Leu Phe Trp Leu Ala Cys Glu Asp Leu Lys Lys Glu Gln 115 aac aaa aaa gta att gaa gaa aag gct agg atg ata tat gaa gat tac 913 Asn Lys Lys Val Ile Glu Glu Lys Ala Arg Met Ile Tyr Glu Asp Tyr 130 135 125 961 att tct ata cta tca cca aaa gag gtc agt ctt gat tct cga gtt aga Ile Ser Ile Leu Ser Pro Lys Glu Val Ser Leu Asp Ser Arg Val Arg 145 150 1009 gag gtg atc aat aga aat ctg ttg gat ccc aat cct cac atg tat gaa Glu Val Ile Asn Arq Asn Leu Leu Asp Pro Asn Pro His Met Tyr Glu 160 165 gat gcc caa ctt cag ata tat act tta atg cac aga gat tct ttt cca 1057 Asp Ala Gln Leu Gln Ile Tyr Thr Leu Met His Arg Asp Ser Phe Pro 175 180 185 agg ttt ttg aac tct caa att tat aag tca ttt gtt gaa agt act gct 1105 Arg Phe Leu Asn Ser Gln Ile Tyr Lys Ser Phe Val Glu Ser Thr Ala 190 195 ggc tct tct tct gaa tct taa tg ttcatttaaa aacaatcatt ttggagggct 1158 Gly Ser Ser Ser Glu Ser gagatgggaa ataaaagtag ttaaataaca tcagaaactg agttcctgga gaactacagt 1218 ttagcattcc tcaggctact gtgaaaacac aaccgttatg gtctttgtct ccatttttat 1278 1338 caaggttttc catggttaag tttggagaaa ataccacaca aaacaatgaa ttgccaaatt 1398 gtttgtttta ttcaagactc attctacttg caagcaaagt gtatttgtag tcctatgaac 1458 agtetecteg tgtateteca gagactgeat gtgcaaagta aaatgettea tttgccacat agttgttgta atatttaatc cagtagcata acttatatct gtatttaagg acttttgtgc 1518 aatatggtct taagaaataa ttgccaaaaa aatcggccat gggttgcatt ttttaacata 1578 atctaagacc caaaaaaaag catttttact atggaacaat ggtattcaac aatctatata 1638 ctgtgtttag taccctaatt tttgagccaa tatttctgta ccttaaaaaa aactatttat 1698 ctttgtttgt tggaaaaacc taatggggaa tcctctggtg gtccttgcca aaactgtgga 1758 1813 tttttctttc cgggaaagtt tcctttgcct aaagccccaa acccaaaaaa aaaaa

85

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Ser	Ser	Pro	_	Glu	Lys	Leu	Ile		Arg	Asp	Ile	Ala		Thr	Tyr	
			150					155					160			702
		cac His 165														703
		aac Asn														751
	-	cag Gln														799
		gag Glu														847
	_	cgg Arg						~	_	_					_	895
		cag Gln 245														943
		ttc Phe	_			~					-		_	-		991
		ctc Leu		_		_										1039
	_	ttt Phe	-			_										1087
		ctc Leu														1135
		gag Glu 325														1183
		agc Ser														1231
		ccc Pro														1279
		aag Lys														1327

	375	380		385
			acc cta gag aag Thr Leu Glu Lys 400	
	Asp Arg Leu 1		caa gtg aca cgg Gln Val Thr Arg 415	
			gag ctg gcg gtg Glu Leu Ala Val 430	
cag cag tgc agc Gln Gln Cys Ser 435	tcg gcg gcc g Ser Ala Ala (440	gag gac ctg Glu Asp Leu	cag aag gca cag Gln Lys Ala Gln 445	agc acc 1519 Ser Thr 450
			ccc cgc ctc aca Pro Arg Leu Thr	
			cag tcg agg ctg Gln Ser Arg Leu 480	
	Gly Ala Leu A		cag gac aag gtt Gln Asp Lys Val 495	
			gag aac aat gtg Glu Asn Asn Val 510	
			cgg gaa ggc cag Arg Glu Gly Gln 525	
			cag gag ctc tcg Gln Glu Leu Ser	
tgg cag gac cag Trp Gln Asp Gln 550	atc gag gag of Ile Glu Glu I	ctg aag acc Leu Lys Thr 555	gag gtg cgg ctg Glu Val Arg Leu 560	ctg aag 1855 Leu Lys
	Phe Glu Asp 1		ttc gat ggg ctg Phe Asp Gly Leu 575	
			tcg tcg gac gag Ser Ser Asp Glu 590	
ctt ggc gta ggc Leu Gly Val Gly 595	gtg ggc gct g Val Gly Ala 2 600	gcc ctg cag Ala Leu Gln	gac gca ttg tac Asp Ala Leu Tyr 605	cct ctg 1999 Pro Leu 610

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tac ggc agg aag att ctt ttg ctg ttt gca gcc aat tgg gat cag agt Tyr Gly Arg Lys Ile Leu Leu Phe Ala Ala Asn Trp Asp Gln Ser 140 145 150	783
agg aac tcc ttc aca gac atc ctt cgt gcc atc ctg ctg tca ttg gaa Arg Asn Ser Phe Thr Asp Ile Leu Arg Ala Ile Leu Leu Ser Leu Glu 155 160 165	831
gtc cta atc gaa gat ccg gag ctt cag ata aat ggc ttc att tta att Val Leu Ile Glu Asp Pro Glu Leu Gln Ile Asn Gly Phe Ile Leu Ile 170 175 180	879
ata gac tgg agt aat ttt tcc ttc aaa caa gcc tcc aaa ctg aca cct Ile Asp Trp Ser Asn Phe Ser Phe Lys Gln Ala Ser Lys Leu Thr Pro 185 190 195	927
tca atc ctt aaa ctg gcc att gaa ggg ttg cag gac agc ttt cct gcc Ser Ile Leu Lys Leu Ala Ile Glu Gly Leu Gln Asp Ser Phe Pro Ala 200 205 210 215	975
cgc ttt gga gga gtc cac ttt gtc aac cag ccc tgg tac att cat gcc Arg Phe Gly Val His Phe Val Asn Gln Pro Trp Tyr Ile His Ala 220 225 230	1023
ctc tac aca ctc atc aag cca ttt ctt aaa gac aag acc agg aaa cgg Leu Tyr Thr Leu Ile Lys Pro Phe Leu Lys Asp Lys Thr Arg Lys Arg 235 240 245	1071
att ttc ctg cat gga aac aat tta aac agc ctt cac cag cta ata cac Ile Phe Leu His Gly Asn Asn Leu Asn Ser Leu His Gln Leu Ile His 250 255 260	1119
cct gaa ttt ttg ccc tct gaa ttt gga gga act ctt cct ccc tta tga Pro Glu Phe Leu Pro Ser Glu Phe Gly Gly Thr Leu Pro Pro Leu * 265 270 275	1167
catgggaact tgggcccgga cgttactcgg tcccgactac agcgatgaaa atgactatac	1227
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agtcagattc tgactctgca tacccctcca atg gct ttc gcc acc ccc aaa Met Ala Phe Ala Thr Pro Lys 1 5	171
tca ctt gga gta aaa gcc gaa gtc ctt cca gca gct tac cag gtg ctg Ser Leu Gly Val Lys Ala Glu Val Leu Pro Ala Ala Tyr Gln Val Leu 10 15 20	219
cat gat cca gac tcc ttc tta gcc ctc tgg ctc tcc tgc tgc tct cct His Asp Pro Asp Ser Phe Leu Ala Leu Trp Leu Ser Cys Cys Ser Pro 25 30 35	267
tct tca ttt ctc tct agc cac acc agc ttt ctt gct gag agc act ggg Ser Ser Phe Leu Ser Ser His Thr Ser Phe Leu Ala Glu Ser Thr Gly 40 45 50 55	315
tgc tct gtc tac act att ctc caa aat atc cat atg gtt tgt cct cct Cys Ser Val Tyr Thr Ile Leu Gln Asn Ile His Met Val Cys Pro Pro 60 65 70	363
tca ttt act ttc ttg aat tcc acg gtc tca gtg aga tta cct tgg cat Ser Phe Thr Phe Leu Asn Ser Thr Val Ser Val Arg Leu Pro Trp His 75 80 85	411
cct agt taa agctgct gcctgtcctc tcaccctgcg tcctgcagtc ccctttctag Pro Ser * 90	467
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cagccgccag cgcgccccgt cggcagctct ccatctgcac gtctctccgt gaaccccgtg	180
agcggtgtgc agccacc atg ttc agc tgg ctg aag cgg ggc ggg gca cgg Met Phe Ser Trp Leu Lys Arg Gly Gly Ala Arg 1 5 10	230
ggc cag cag ccc gag gcc atc cgc acg gtg acc tcg gcc ctc aag gag Gly Gln Gln Pro Glu Ala Ile Arg Thr Val Thr Ser Ala Leu Lys Glu 15 20 25	278
ctg tac cgc acg aag ctg ctg ccg ctg gag gag cac tac cgc ttt ggg Leu Tyr Arg Thr Lys Leu Leu Pro Leu Glu Glu His Tyr Arg Phe Gly 30 35 40	326
gcc ttc cac tcg ccg gcc ctg gag gac gca gac ttc gac ggc aag ccc Ala Phe His Ser Pro Ala Leu Glu Asp Ala Asp Phe Asp Gly Lys Pro 45 50 55	374
atg gtg ctg gtg gcc ggc cag tac agc acg ggc aag acc agc ttc atc Met Val Leu Val Ala Gly Gln Tyr Ser Thr Gly Lys Thr Ser Phe Ile 60 65 70 75	422
cag tac ctg ctg gag cag gag gtg ccc ggc tcc cgc gtg ggg cct gag Gln Tyr Leu Leu Glu Gln Glu Val Pro Gly Ser Arg Val Gly Pro Glu 80 85 90	470
ccc acc acc gac ttc ttt gtg gcc gtc atg cac ggg gac act gag ggc Pro Thr Thr Asp Phe Phe Val Ala Val Met His Gly Asp Thr Glu Gly 95 100 105	518
acc gtg ccc ggc aac gcc ctc gtc gtg gac ccg gac aag ccc ttc cgc Thr Val Pro Gly Asn Ala Leu Val Val Asp Pro Asp Lys Pro Phe Arg 110 115 120	566
aaa ctc aac cct ttc gga aac acc ttc ctc aac agg ttc atg tgt gcc Lys Leu Asn Pro Phe Gly Asn Thr Phe Leu Asn Arg Phe Met Cys Ala 125 130 135	614
cag ctc cct aat cag gtc ctg gag agc atc agc atc atc gac acc ccg Gln Leu Pro Asn Gln Val Leu Glu Ser Ile Ser Ile Ile Asp Thr Pro 140 145 150 155	662
ggt atc ctg tcg ggt gcc aag cag aga gtg agc cgc ggc tac gac ttc Gly Ile Leu Ser Gly Ala Lys Gln Arg Val Ser Arg Gly Tyr Asp Phe 160 165 170	710
ccg gcc gtg ctg cgc tgg ttc gcg gag cgc gtg gac ctc atc atc ctg Pro Ala Val Leu Arg Trp Phe Ala Glu Arg Val Asp Leu Ile Ile Leu 175 180 185	758

				aag Lys								806
				ggc Gly								854
				gag Glu 225								902
	_	 -	_	ggc Gly	-							950
_		-		ttc Phe		-			-		_	998
				ctg Leu								1046
				gca Ala								1094
	_	 _		cga Arg 305	-	_			_			1142
				gtg Val								1190
		_		gtc Val			_	_	_	-		1238
				ttt Phe								1286
				acc Thr								1334
				atg Met 385								1382
				gag Glu								1430

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tgg gtg gtg acc aaa gac aag tcc aaa tac gac gag atc ttc tac aac Trp Val Val Thr Lys Asp Lys Ser Lys Tyr Asp Glu Ile Phe Tyr Asn 445 450 455	1574
ctg gcg cct gcc gac ggc aag ctg agc ggc tcc aag gcc aag acc tgg Leu Ala Pro Ala Asp Gly Lys Leu Ser Gly Ser Lys Ala Lys Thr Trp 460 465 470 475	1622
atg gtg ggg acc aag ctc ccc aac tca gtg ctg ggg cgc atc tgg aag Met Val Gly Thr Lys Leu Pro Asn Ser Val Leu Gly Arg Ile Trp Lys 480 485 490	1670
ctc agc gat gtg gac cgc gac ggc atg ctg gat gat gaa gag ttc gcg Leu Ser Asp Val Asp Arg Asp Gly Met Leu Asp Asp Glu Glu Phe Ala 495 500 505	1718
ctg gcc agc cac ctc atc gag gcc aag ctg gaa ggc cac ggg ctg ccc Leu Ala Ser His Leu Ile Glu Ala Lys Leu Glu Gly His Gly Leu Pro 510 515 520	1766
gcc aac ctg ccc cgt cgc ctg gtg cca ccc tcc aag cga cgc cac aag Ala Asn Leu Pro Arg Arg Leu Val Pro Pro Ser Lys Arg Arg His Lys 525 530 535	1814
ggc tcc gcc gag tga gccgggcccc cctcccatgg ccctgctgtg gctccccagc Gly Ser Ala Glu * 540	1869
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tcattcaaat atttattgag cacctactat gtgcccagcc ctgttctagg cactgggcat	2169
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gagggcacct acacagtcac gcaaacacac actaattcct ggcagggccc ccagccctc	2289
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etgteegetg ecaagggaag tgacageege ageegggete teageeageg geegggegee 180

eegeeggaee atg ete tee agt aeg eag aac geg gge gge tee tat eag 228

Met Leu Ser Ser Thr Gln Asn Ala Gly Gly Ser Tyr Gln

			ctt Leu						276	5
			aaa Lys 35						324	4
			aga Arg						372	2
			ttc Phe						420	Э
 _	_	-	tta Leu					_	468	8
			gca Ala						510	б
			aaa Lys 115						564	4
			ttg Leu						612	2
			gaa Glu						660	0
			ctt Leu						708	8
			cgt Arg						756	6
			ctg Leu 195						804	4
			ttt Phe						852	2
			gac Asp						900	0

ttt tca aat cct aat ggc cgt ata tct cct ttg gca aga gct ggg tcc Phe Ser Asn Pro Asn Gly Arg Ile Ser Pro Leu Ala Arg Ala Gly Ser 240 245 250	948
agc agt gtt agc agg ggt ggc agt cct tgt gtt tgt tat acc aat aaa Ser Ser Val Ser Arg Gly Gly Ser Pro Cys Val Cys Tyr Thr Asn Lys 255 260 265	996
tgc ttt agc tgc aac taa aataaa aaagttaaag gtaaaaaaat gactgcctca Cys Phe Ser Cys Asn * 270 275	1050
tgttacatgt gtcaaacagg agctgagttt tctgacttga gttaacaatc accatctcgc	1110
taattatata gagagagtta caaatggaag tcatcgaatt ttatcattta cttattcact	1170
caaccagtat tgaacaagca tgtatcttat gtcagccagt gtttcaggca caggaagtac	1230
agcagtgagg ggaaatgaca agtccagctc tcatgagggg tagtggagga gacaggcatt	1290
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cac caa ccc cat aaa gtg aca cag tac aag aag ggc aag gat tct ctg His Gln Pro His Lys Val Thr Gln Tyr Lys Lys Gly Lys Asp Ser Leu 20 25 30	154
tac gcc cag gga aag cgg cgt tat gac agg aag cag agt ggc tat ggt Tyr Ala Gln Gly Lys Arg Arg Tyr Asp Arg Lys Gln Ser Gly Tyr Gly 35 40 45	202
ggg caa act aag ccg att ttc cgg aaa aag gct aaa act aca aag aag Gly Gln Thr Lys Pro Ile Phe Arg Lys Lys Ala Lys Thr Thr Lys Lys	250

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atg ctg gct att aaa aga tgc aag cat ttt gaa ctg gga gga gat aag Met Leu Ala Ile Lys Arg Cys Lys His Phe Glu Leu Gly Gly Asp Lys 85 90 95	346
aag aga aag gta tat aat tat ggg tcg gaa ggt gca atc ttt ctc ata Lys Arg Lys Val Tyr Asn Tyr Gly Ser Glu Gly Ala Ile Phe Leu Ile 100 105 110	394
gct tta tta ttt cga aaa ggt gaa cat cta ttc ctt gtg gca tag agc Ala Leu Leu Phe Arg Lys Gly Glu His Leu Phe Leu Val Ala * 115 120 125	442
tcaggggtaa tcctctaaaa atattagatc tatagctaaa gatatgtgag gtcttttgct	502
acaaggagga aaggaagaat gaggaagctt aacagcatgg tgactatttt aggaacagat	562
aatgttetta atggggeagt agtteatgge aaaatacaaa acaaettttt tetgttetge	622
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cct gcc aac tct gag gaa ggc cag gaa ctt tat gtc tgc aca gtc aag Pro Ala Asn Ser Glu Glu Gly Gln Glu Leu Tyr Val Cys Thr Val Lys 10 15 20	163
gat gat gtg aac ttg gat aca gta ctt ctc cta ccc ttt ttg aaa gaa Asp Asp Val Asn Leu Asp Thr Val Leu Leu Pro Phe Leu Lys Glu 25 30 35	211
ata gca gta agc caa ctg gat caa ctg agc cca gag gaa cag ttg ctg Ile Ala Val Ser Gln Leu Asp Gln Leu Ser Pro Glu Glu Gln Leu Leu	259

						att Ile 60										307
_			_			tgg Trp	_			_				-	-	355
						cat His										403
			_			ata Ile		_					-			451
						aag Lys										499
					_	gaa Glu 140					_	•	_	_		547
						cac His										595
						gta Val	-	-			-	_	_	_	_	643
						cta Leu								taa *	gca	691
tgct	gggg	jtc a	acgto	gtcat	g ca	aaco	ttgg	g aca	agato	gact	gaac	cctct	ct a	tgco	cttggt	751
ttct	tcat	ct g	gtgta	gaco	jc ca	igtga	cgat	gto	ctcct	tcc	tcag	gtc	ggg g	gacta	ıtctgg	811
gaco	caag	ıgt t	ct													824

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tccctcctcc cccttcac atg gca tca tcg acc Met Ala Ser Ser Thr 1	tcc ctc cca gct Ser Leu Pro Ala	cct ggc tct	t cgg cct aag aag	238 286
cct cta ggc aag atg Pro Leu Gly Lys Met 20		Arg Gln Thr		334
ccc aag aag agg ccc Pro Lys Lys Arg Pro 35		=		382
cag cct acc tca cag Gln Pro Thr Ser Gln 50		-	r Leu Ser Ser Val	430
acg tct ccc agc ctg Thr Ser Pro Ser Leu 65				478
cgc tgg agc aaa gac Arg Trp Ser Lys Asp 85	Tyr Asp Val Cys			526
ctg gtg gcc gcc cag Leu Val Ala Ala Gln 100		Tyr Leu Glu		574
agc ctg cgc tgc ttc Ser Leu Arg Cys Phe 115	-			622
ata gtg tcc gag ctg Ile Val Ser Glu Leu 130			r His Cys Arg Val	670
ctg ctc atc acg ccg Leu Leu Ile Thr Pro 145				718
atg ctg cag gcc ctg Met Leu Gln Ala Leu 165	Thr Glu Ala Pro			766
ccc ctg ctg tcg ggc Pro Leu Leu Ser Gly 180		Ala Tyr Pro		814
ttc atg tac tac gtc Phe Met Tyr Tyr Val 195		-		862

Val Lys Glu Ala Val Met Arg Cys Lys Leu Leu Gln Glu Gly Glu Gly 210 215 220	910
gaa cgg gat tca gct aca gta ttt gat cta ctt tga cttt taggagacag Glu Arg Asp Ser Ala Thr Val Phe Asp Leu Leu * 225 230 235	960
ccctgtagcc tagtagttca aagcgcagct tctggaagag gctgtcgggg tttgtatcct	1020
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atctggattt gagacggagc acggaacatt tcactcaggg gaagagct atg aac atg Met Asn Met 1	177
ctg act gcc agc ctg ttg agg gca gtc ata gcc tcc atc tgt gtt gta Leu Thr Ala Ser Leu Leu Arg Ala Val Ile Ala Ser Ile Cys Val Val	
5 10 15	225
tcc agc atg gct cag aag gta act caa gcg cag act gaa att tct gtg Ser Ser Met Ala Gln Lys Val Thr Gln Ala Gln Thr Glu Ile Ser Val 20 25 30 35	225 273
tcc agc atg gct cag aag gta act caa gcg cag act gaa att tct gtg Ser Ser Met Ala Gln Lys Val Thr Gln Ala Gln Thr Glu Ile Ser Val	
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tcc agc atg gct cag aag gta act caa gcg cag act gaa att tct gtg Ser Ser Met Ala Gln Lys Val Thr Gln Ala Gln Thr Glu Ile Ser Val 20 25 30 35 gtg gag aag gag gat gtg acc ttg gac tgt gtg tat gaa acc cgt gat Val Glu Lys Glu Asp Val Thr Leu Asp Cys Val Tyr Glu Thr Arg Asp 40 45 50 act act tat tac tta ttc tgg tac aag caa cca cca agt gga gaa ttg Thr Thr Tyr Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Gly Glu Leu	273 321

acc atc aca gcc tca caa gtc gtg gac tca gca gta tac ttc tgt gct Thr Ile Thr Ala Ser Gln Val Val Asp Ser Ala Val Tyr Phe Cys Ala 100 105 110 115	513
ctg agt gag gcg gcc caa gaa acc agt ggc tct agg ttg acc ttt ggg Leu Ser Glu Ala Ala Gln Glu Thr Ser Gly Ser Arg Leu Thr Phe Gly 120 125 130	561
gaa gga aca cag ctc aca gtg aat cct gat atc cag aac cct gac cct Glu Gly Thr Gln Leu Thr Val Asn Pro Asp Ile Gln Asn Pro Asp Pro 135 140 145	609
gcc gtg tac cag ctg aga gac tct aaa tcc agt gac aag tct gtc tgc Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys 150 155 160	657
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tct gat gtg tat atc aca gac aaa ctg tgc tag actgtgag gctagggatt Ser Asp Val Tyr Ile Thr Asp Lys Leu Cys * 180 185 190	756
tcagaaccac cgggttgggc ctggagcaac aaatctgact ttgcatgggc aacgccttca	816
acaacaggct tatttcagaa gaaccettet teeccageee caaaaggtee ettgatggea	876
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	40					45					50						
														cac His		:	247
														aag Lys 85			295
														ttc Phe			343
ccc Pro	aag Lys	tgc Cys 105	gac Asp	gag Glu	aac Asn	ggc Gly	aac Asn 110	tat Tyr	ctg Leu	cca Pro	ctc Leu	cag Gln 115	tgc Cys	tat Tyr	GJÀ aaa		391
														gtc Val			439
aac Asn 135	acc Thr	aga Arg	agc Ser	cgc Arg	ggg Gly 140	cac His	cat His	aac Asn	tgc Cys	agt Ser 145	gag Glu	tca Ser	ctg Leu	gaa Glu	ctg Leu 150		487
gag Glu	gac Asp	ccg Pro	tct Ser	tct Ser 155	ggg	ctg Leu	ggt Gly	gtg Val	acc Thr 160	aag Lys	cag Gln	gat Asp	ctg Leu	ggc Gly 165	cca Pro		535
	ccc Pro		tga * 170	gag	cago	caga	ggc (ggtc	tcaa	ac at	teet	gcca	g cc	ccaca	acag		590
ctac	cagct	tt d	cttg	ctcc	ct to	cagc	ccca	a gc	ccct	cccc	cato	ctcc	cac (cctg	acctc		650
atco	ccato	gag a	accci	tggt	gc ct	-ggc	tctti	t cg1	tcac	cctt	gga	caag	aca (aacca	aagtcg		710
gaad	cagca	aga t	taaca	aatg	ca go	caag	gccct	t gci	tgcc	caat	ctc	catc	tgt (caaca	aggggc		770
ggto	cgac	gcg (gccg	cgaai	tt c	ggato	cctc	g aga	agato	ctct	ttt	tttg	ggt	ttgg	ggggt		830
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tttggatttt taatttctag atttggcaat tcttcgctga agtcatc atg agc ttt Met Ser Phe 1	176
ttc caa ctc ctg atg aaa agg aag gaa ctc att ccc ttg gtg gtg ttc Phe Gln Leu Leu Met Lys Arg Lys Glu Leu Ile Pro Leu Val Val Phe 5 10 15	224
atg act gtg gcg gcg ggt gga gcc tca tct ttc gct gtg tat tct ctt Met Thr Val Ala Ala Gly Gly Ala Ser Ser Phe Ala Val Tyr Ser Leu 20 25 30 35	272
tgg aaa acc gat gtg atc ctt gat cga aaa aaa aat cca gaa cct tgg Trp Lys Thr Asp Val Ile Leu Asp Arg Lys Lys Asn Pro Glu Pro Trp 40 45 50	320
gaa act gtg gac cct act gta cct caa aag ctt ata aca atc aac caa Glu Thr Val Asp Pro Thr Val Pro Gln Lys Leu Ile Thr Ile Asn Gln 55 60 65	368
caa tgg aaa ccc att gaa gag ttg caa aat gtc caa agg gtg acc aaa Gln Trp Lys Pro Ile Glu Glu Leu Gln Asn Val Gln Arg Val Thr Lys 70 75 80	416
tga cgag ccctcgcctc tttcttctga agagtactct ataaatctag tggaaacatt *	473
tctgcacaaa ctagattctg gacaccagtg tgcggaaatg cttctgctac atttttaggg	533
tttgtctaca ttttttgggc tctggataag gaattaaagg agtgcagcaa taactgcact	593
gtctaaaagt ttgtgcttat tttcttgtaa atttgaatat tgcatattga aatttttgtt	653
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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (50)..(1060)

<400> 238

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													cgg Arg			199
													tat Tyr			247
		_	-	_			-	-	_	-			gtg Val 80			295
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													agg Arg			391
													acc Thr			439
													tat Tyr			487
													ata Ile 160			535
	_							_	_	_			tgg Trp	_		583
													ccg Pro			631
													gtg Val			679
aag		cca	act	ata	aaa	acc	cta	atσ	aaa	cat	ctc	aat	ata	cta	taa	727

acg ctg ctg gtg tcc cgc tgg ttc atc tgc ctg ttt gtg gac atc ttg 775 Thr Leu Leu Val Ser Arg Trp Phe Ile Cys Leu Phe Val Asp Ile Leu 235 230 823 ccc qtq qaq aca gtg ctt cgg atc tgg gac tgt ttg ttt aac gaa ggc Pro Val Glu Thr Val Leu Arg Ile Trp Asp Cys Leu Phe Asn Glu Gly 250 245 tcg aag att atc ttc cgg gtg gcc ctg acc tta att aag cag cac cag 871 Ser Lys Ile Ile Phe Arg Val Ala Leu Thr Leu Ile Lys Gln His Gln 260 265 919 gag ttg att ttg gaa gcc acc agc gtt cca gac att tgc gat aag ttt Glu Leu Ile Leu Glu Ala Thr Ser Val Pro Asp Ile Cys Asp Lys Phe 280 285 967 aag cag ata acc aaa ggg agt ttc gtg atg gag tgt cac acg ttt atg Lys Gln Ile Thr Lys Gly Ser Phe Val Met Glu Cys His Thr Phe Met 1015 cag aaa ata ttt tca gaa cct gga agc tta tcc atg gcc acc gtc gcc Gln Lys Ile Phe Ser Glu Pro Gly Ser Leu Ser Met Ala Thr Val Ala 310 315 1063 aag ctc cgc gag agc tgc agg gcc cgg ctg ctg gca cag ggg tga gcg Lys Leu Arg Glu Ser Cys Arg Ala Arg Leu Leu Ala Gln Gly 325 330 tgcctgtccc ctgcgttgct cgtctctaca ctgacgatgc ccctttccag agttgacact 1123 1183 ggaccaactt tcactgcttt cctttttagt gttgtaaata cttgacatca ctacacttta gttgtgaatt ttttaaaaga gcagtttaaa atcaggtcat tctaccagct tttgatgatt 1243 agctatgaag tcatactttt taaagaaaac ttatttttac ctgagagatc aataatatat 1303 aaaatgtgag tgtgggtttg tatctaataa agtatgccaa cacctgtgtt tgtgatcagt 1363 1395 ttctcagctg actggaaatt aaaaaaaaaa aa

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<211> 526

<212> DNA

<213> Homo sapiens

<220>

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<222> (187)..(324)

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gaaaagcttg cagaatttct tctgaaatta cttaaaatta ctgtatgcat aaacttacaa	180
aaacat atg cta tac caa ggc aga gaa aag aaa aaa agt gaa gtg gct Met Leu Tyr Gln Gly Arg Glu Lys Lys Lys Ser Glu Val Ala 1 5 10	228
aca aag gtc cct ggg gca tca cct gct cac cta gga acc agg agt act Thr Lys Val Pro Gly Ala Ser Pro Ala His Leu Gly Thr Arg Ser Thr 15 20 25 30	276
gga tac tgt tcc gtt act ggt aac cta tct gga tgt aaa ggt tca taa Gly Tyr Cys Ser Val Thr Gly Asn Leu Ser Gly Cys Lys Gly Ser * 35 40 45	324
gttacaatgc tttttttgtt taaaaaaaaa aaaaagtctg tactttacaa gccaaaagtg	384
aaaatgccac acatcctctt tacgctttca tgtacactaa gtcactccat ttggttgata	444
ccaataatga tagctcctgt gtataatatt ttcataaatc atactcagta agcaaatctc	504
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gag gaa gac cac gcg gag gag ccc tcc aag gac ggc ggt gcc ctg gag Glu Glu Asp His Ala Glu Glu Pro Ser Lys Asp Gly Gly Ala Leu Glu 10 15 20 25	101
gag aag gat tcg gac ggg gca gcc tcc aag gag gac agc ggc ccc agc Glu Lys Asp Ser Asp Gly Ala Ala Ser Lys Glu Asp Ser Gly Pro Ser 30 35 40	149
acc agg cag gct tca gga gag gcc tcc tcg ctg cgg gac tac gcg gcc Thr Arg Gln Ala Ser Gly Glu Ala Ser Ser Leu Arg Asp Tyr Ala Ala 45 50 55	197
tcc acc atg acc gag ttc ctc ggc atg ttt ggc tat gat gac cag aac Ser Thr Met Thr Glu Phe Leu Gly Met Phe Gly Tyr Asp Asp Gln Asn	245

														cac His		293
														tcc Ser		341
														tac Tyr 120		389
														agc Ser		437
														ccc Pro		485
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														gta Val		581
														ggc Gly 200		629
														aag Lys		677
														gag Glu		725
agc Ser	ccc Pro 235	gac Asp	atg Met	ggc Gly	ggg Gly	gcc Ala 240	atc Ile	gcc Ala	ttc Phe	aag Lys	aca Thr 245	ggc Gly	aag Lys	gtg Val	Gly	773
														ccc Pro		821
														agc Ser 280		869
														gcc Ala		917
ctg	tcc	ttc	aac	act	ccc	gag	tac	ctg	aag	tca	acc	ttc	tcc	aaa	aca	965

Leu	Ser	Phe 300	Asn	Thr	Pro	Glu	Tyr 305	Leu	Lys	Ser	Thr	Phe 310	Ser	Lys	Thr	
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aca Thr 330	gat Asp	aaa Lys	cca Pro	gcc Ala	gtc Val 335	act Thr	gaa Glu	gat Asp	gta Val	aac Asn 340	att Ile	tac Tyr	cag Gln	aaa Lys	tat Tyr 345	1061
att Ile	gcc Ala	agg Arg	ttc Phe	tcg Ser 350	ggc Gly	agc Ser	cag Gln	cac His	tgt Cys 355	ggc Gly	cac His	atc Ile	cac His	tgt Cys 360	gcc Ala	1109
tac Tyr	cag Gln	tac Tyr	cgc Arg 365	gag Glu	cac His	tac Tyr	cac His	tgc Cys 370	ctt Leu	gac Asp	cct Pro	gag Glu	tgt Cys 375	aac Asn	tac Tyr	1157
cag Gln	agg Arg	ttc Phe 380	acg Thr	agt Ser	aag Lys	cag Gln	gac Asp 385	gtg Val	atc Ile	cgc Arg	cac His	tac Tyr 390	aac Asn	atg Met	cac His	1205
aag Lys	aag Lys 395	cgc Arg	gac Asp	aac Asn	tcc Ser	ctg Leu 400	cag Gln	cac His	ggc Gly	ttc Phe	atg Met 405	cgt Arg	ttc Phe	agc Ser	ccg Pro	1253
ctg Leu 410	gac Asp	gac Asp	tgc Cys	agc Ser	gtc Val 415	tac Tyr	tac Tyr	cac His	ggc Gly	tgc Cys 420	cac His	ctc Leu	aat Asn	ggg Gly	aag Lys 425	1301
agc Ser	acc Thr	cac His	tat Tyr	cac His 430	tgc Cys	atg Met	cag Gln	gtg Val	ggc Gly 435	tgt Cys	aac Asn	aag Lys	gtg Val	tac Tyr 440	acg Thr	1349
agc Ser	acg Thr	tct Ser	gac Asp 445	gtg Val	atg Met	acc Thr	cac His	gag Glu 450	aac Asn	ttc Phe	cac His	aag Lys	aag Lys 455	aat Asn	acc Thr	1397
cag Gln	ctc Leu	att Ile 460	aac Asn	gac Asp	ggc Gly	ttc Phe	cag Gln 465	cgc Arg	ttc Phe	cga Arg	gcc Ala	acc Thr 470	gaa Glu	gac Asp	tgt Cys	1445
ggc Gly	aca Thr 475	gcc Ala	gac Asp	tgc Cys	cag Gln	ttc Phe 480	tac Tyr	gga Gly	cag Gln	aag Lys	acc Thr 485	acg Thr	cac His	ttc Phe	cac His	1493
tgc Cys 490	Arg	cgc Arg	ccc Pro	ggc	tgc Cys 495	aca Thr	ttc Phe	act Thr	ttc Phe	aag Lys 500	aac Asn	aag Lys	tgt Cys	gac Asp	atc Ile 505	1541
gag Glu	aag Lys	cac His	aag Lys	agc Ser 510	Tyr	cac His	atc Ile	aag Lys	gac Asp 515	gat Asp	gcc Ala	tac Tyr	gcc Ala	aag Lys 520	gac Asp	1589
ggc Gly	ttc Phe	aag Lys	aag Lys	ttc Phe	tac Tyr	aag Lys	tac Tyr	gag Glu	gag Glu	tgc Cys	aag Lys	tac Tyr	gag Glu	ggc Gly	tgc Cys	1637

			525					530					535				
gtg t Val T	уr	~	_	_						_		_	-			-	1685
ggc t Gly P 5																-	1733
cat g His G 570	_	-				_		_		_						:	1781
tcg c Ser L	_	_		-	_	-	_	-		-	_					- -	1829
gac c Asp L		_	_			~	-	-	~	•			_	_	-	:	1877
gcc to Ala So	er			_	_	-					-	-	-	_		:	1925
gcc gc Ala A 63																-	1973
atc to Ile So 650																2	2021
ctg go Leu A					_	~ ~	_				-					2	2069
ata c Ile L	_	-														2	2117
ctc c	eu		~		_				_	-		_			-	2	2165
aca co Thr P:		_	-	_	_	-										2	2213
gcc go Ala A 730																2	2261
gca ag Ala S																2	2309

gcc Ala	ctc Leu	aag Lys	ccc Pro 765	tct Ser	gcc Ala	acc Thr	ttt Phe	gac Asp 770	cca Pro	gga Gly	agc Ser	ggg Gly	cag Gln 775	cag Gln	gtc Val	2357
acc Thr	cca Pro	gcc Ala 780	agg Arg	ttc Phe	ccc Pro	ccg Pro	gcc Ala 785	caa Gln	gtg Val	aag Lys	ccg Pro	gaa Glu 790	ccc Pro	ggt Gly	gag Glu	2405
agc Ser	acc Thr 795	ggc Gly	gcc Ala	cca Pro	ggc Gly	ccc Pro 800	cac His	gaa Glu	gcc Ala	tcc Ser	cag Gln 805	gac Asp	cgc Arg	agt Ser	cta Leu	2453
gac Asp 810	ctg Leu	act Thr	gtg Val	aag Lys	gag Glu 815	ccc Pro	agc Ser	aac Asn	gaa Glu	tca Ser 820	aat Asn	ggc Gly	cac His	gca Ala	gtc Val 825	2501
ccg Pro	gca Ala	aat Asn	tca Ser	tct Ser 830	ctt Leu	tta Leu	tcc Ser	tcg Ser	ctt Leu 835	atg Met	aat Asn	aag Lys	atg Met	tct Ser 840	cag Gln	2549
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agg Arg 890	ttt Phe	ggt Gly	aca Thr	aag Lys	gac Asp 895	ttc Phe	tgt Cys	gac Asp	ggc Gly	cag Gln 900	tgt Cys	gac Asp	ttc Phe	ctc Leu	cac His 905	2741
aag Lys	gcc Ala	cac His	ttc Phe	cac His 910	tgc Cys	gtg Val	gtg Val	gag Glu	gaa Glu 915	tgc Cys	ggc	gcg Ala	ctc Leu	ttc Phe 920	agc Ser	2789
acc Thr	ttg Leu	gac Asp	ggg Gly 925	gcc Ala	atc Ile	aag Lys	cac His	gca Ala 930	aac Asn	ttc Phe	cac His	ttc Phe	cgg Arg 935	Thr	gag Glu	2837
gga Gly	gga Gly	gca Ala 940	Ala	aaa Lys	gga Gly	aac Asn	aca Thr 945	gag Glu	gct Ala	gcc Ala	ttt Phe	ccg Pro 950	Ala	tcg Ser	gcc Ala	2885
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gtc Val 970	Thr	acg Thr	gcc Ala	acg Thr	gtg Val 975	Ser	tct Ser	ctg Leu	gag Glu	980 980	Pro	gct Ala	ccc Pro	agc Ser	ccg Pro 985	2981

gcc tcc gtg ccc Ala Ser Val Pro	tcc acc ccc acc Ser Thr Pro Thr 990	ctg ctc gcc Leu Leu Ala 995	tgg aag cag ctg gct Trp Lys Gln Leu Ala 1000	3029
tcc acc ata ccc Ser Thr Ile Pro 1005	Gln Met Pro Gln	atc cca gcg Ile Pro Ala 1010	tca gtg cct cac ctg Ser Val Pro His Leu 1015	3077
ccc gcc tcg ccc Pro Ala Ser Pro 1020	ttg gca acg act Leu Ala Thr Thr 1025	Ser Leu Glu	aac gcc aag ccc cag Asn Ala Lys Pro Gln 1030	3125
gtc aaa ccc gga Val Lys Pro Gly 1035	ttc ctc cag ttc Phe Leu Gln Phe 1040	Gln Glu Lys	tga gtcc ctcgatgagc * 1045	3175
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<211> 2450

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<213> Homo sapiens

<220>

<221> CDS

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gcc Ala 30	Tyr	aga Arg	ggt Gly	cat His	ctg Leu 35	cag Gln	cgc Arg	acc Thr	tat Tyr	cag Gln 40	tac Tyr	gcc Ala	tgg Trp	gcg Ala	aat Asn 45	326
gat Asp	gac Asp	ata Ile	tct Ser	gct Ala 50	Leu	act Thr	gca Ala	tcc Ser	aac Asn 55	cta Leu	cta Leu	aaa Lys	aaa Lys	tat Tyr 60	gca Ala	374
gag Glu	aag Lys	tat Tyr	tcc Ser 65	ggc Gly	att Ile	ttg Leu	gaa Glu	ggt Gly 70	cct Pro	gtg Val	gac Asp	cga Arg	ccc Pro 75	gta Val	ctc Leu	422
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Gly ggg	gta Val	gcc Ala	agc Ser 145	aac Asn	ctg Leu	aca Thr	gaa Glu	cct Pro 150	agt Ser	tat Tyr	tca Ser	agt Ser	agt Ser 155	acc Thr	tgt Cys	662
gga Gly	agc Ser	cac His 160	act Thr	gta Val	ccc Pro	agt Ser	ctt Leu 165	cat His	gca Ala	Gly ggg	ctc Leu	cca Pro 170	tct Ser	cag Gln	gaa Glu	710
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tct Ser	Gly ggg	cta Leu	cta Leu	cag Gln 210	ccc Pro	cca Pro	cca Pro	cca Pro	cct Pro 215	cct Pro	ccg Pro	cca Pro	cca Pro	gcc Ala 220	ttg Leu	854
gtc Val	cca Pro	ggc Gly	tac Tyr 225	aat Asn	ggg Gly	act Thr	tct Ser	aac Asn 230	ctc Leu	tcc Ser	agt Ser	tac Tyr	agc Ser 235	tat Tyr	ccg Pro	902

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Gly gag	ggg Gly 255	Ala	ccg Pro	cct Pro	ccg Pro	cct Pro 260	tca Ser	gcg Ala	tac Tyr	ctg Leu	cct Pro 265	Ser	gga Gly	att Ile	cct Pro	998
gct Ala 270	Pro	acc Thr	ccc Pro	cta Leu	ccc Pro 275	ccc Pro	acc Thr	act Thr	gtt Val	cct Pro 280	ggc	tac Tyr	acc Thr	tac Tyr	cag Gln 285	1046
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			agt Ser													1190
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cgg Arg 350	ggg Gly	aat Asn	ggc Gly	ttt Phe	gac Asp 355	aga Arg	agt Ser	gct Ala	gaa Glu	aca Thr 360	tca Ser	tcc Ser	tta Leu	gca Ala	ttt Phe 365	1286
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			agt Ser 385													1382
			gga Gly													1430
			agt Ser													1478
			ggc Gly						Ala							1526
gtg Val	gac Asp	gag Glu	caa Gln	ctg Leu 450	aag Lys	aat Asn	act Thr	gac Asp	acg Thr 455	cac His	ctc Leu	atc Ile	gac Asp	ctg Leu 460	gta Val	1574

							caa Gln								Asp	att Ile	1622
							aag Lys									tgg Trp	1670
E	cca Pro	gtg Val 495	ttg Leu	agg Arg	tca Ser	gac Asp	gcg Ala 500	ttc Phe	agt Ser	gga Gly	ctg Leu	acg Thr 505	gcc Ala	tta Leu	cct Pro	cgg Arg	1718
Ş	igc Ser 510	atc Ile	ctt Leu	tta Leu	ttt Phe	gga Gly 515	cct Pro	cgg Arg	ggg Gly	aca Thr	ggc Gly 520	aaa Lys	aca Thr	tta Leu	ttg Leu	ggc Gly 525	1766
							ctg Leu										1814
							tgg Trp										1862
							agg Arg										1910
a S	gt er	gac Asp 575	att Ile	gac Asp	atg Met	ctt Leu	ctc Leu 580	tcc Ser	tct Ser	caa Gln	gtg Val	aat Asn 585	gag Glu	gaa Glu	cat His	agt Ser	1958
P							acc Thr										2006
							caa Gln										2054
C:	ca ro	gaa Glu	gaa Glu	ata Ile 625	gat Asp	gaa Glu	tcc Ser	ctt Leu	cgg Arg 630	agg Arg	tac Tyr	ttc Phe	atg Met	aaa Lys 635	cga Arg	ctt Leu	2102
t L	ta eu	atc Ile	cca Pro 640	ctt Leu	cct Pro	gac Asp	agc Ser	aca Thr 645	gcg Ala	agg Arg	cac His	cag Gln	ata Ile 650	ata Ile	gta Val	caa Gln	2150
L.	eu	ctc Leu 655	tca Ser	cag Gln	cac His	aat Asn	tac Tyr 660	tgt Cys	ctc Leu	aat Asn	gac Asp	aag Lys 665	gag Glu	ttt Phe	gca Ala	ctg Leu	2198
L	tc eu 70	gtc Val	cag Gln	cgc Arg	aca Thr	gaa Glu 675	ggc Gly	ttt Phe	tct Ser	gga Gly	cta Leu 680	gat Asp	gtg Val	gct Ala	cat His	ttg Leu 685	2246
t	gt	cag	gaa	gca	gtg	gtg	ggc	ccc	ctc	cat	gcc	atg	cca	gcc	aca	gac	2294

Cys Gln Glu Ala Val V 690	al Gly Pro Leu His 695	Ala Met Pro Ala Thr Asp 700
		ccc gtt aca tat caa gac 2342 Pro Val Thr Tyr Gln Asp 715
		agc ata tct caa aag gag 2390 Ser Ile Ser Gln Lys Glu 730
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gcatagtaat gatccaaata	ttcactataa ttgtaaa	gaa acctgaggca attagttaaa 120
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gcatagtaat gatccaaata aagatgcctg taaatcaaat aagtttaag tattcaggca cat aaa aac ttg tat a His Lys Asn Leu Tyr I 5 gga tta tta tca ggg ta Gly Leu Leu Ser Gly Ty	ttcactataa ttgtaaa attcatgata ccttgtt ta atc aaa ata aag le Ile Lys Ile Lys 10 at att aag gtg tta	igaa acctgaggca attagttaaa 120 igaa ataaagc atg cag act 176 Met Gln Thr 1 ttc tac aaa tgg gaa aga 224 Phe Tyr Lys Trp Glu Arg
gcatagtaat gatccaaata aagatgcctg taaatcaaat aagtttaag tattcaggca cat aaa aac ttg tat a His Lys Asn Leu Tyr I 5 gga tta tta tca ggg ta Gly Leu Leu Ser Gly Ty 20 ata att aat tac tca ts	ttcactataa ttgtaaa attcatgata ccttgtt ca atc aaa ata aag le Ile Lys Ile Lys 10 at att aag gtg tta cr Ile Lys Val Leu 25	igaa acctgaggca attagttaaa 120 igaa ataaagc atg cag act 176 Met Gln Thr 1 ttc tac aaa tgg gaa aga 224 Phe Tyr Lys Trp Glu Arg 15 gac tta caa aag aag tgc 272 Asp Leu Gln Lys Lys Cys
aagatgcctg taaatcaaata aagtttaag tattcaggca cat aaa aac ttg tat aa His Lys Asn Leu Tyr I: 5 gga tta tta tca ggg ta Gly Leu Leu Ser Gly Tg 20 ata att aat tac tca ta Ile Ile Asn Tyr Ser Pl 40 aca gat aaa ata aaa ga	ttcactataa ttgtaaa attcatgata ccttgtt ta atc aaa ata aag le Ile Lys Ile Lys 10 at att aag gtg tta yr Ile Lys Val Leu 25 tt aaa att aat tct ne Lys Ile Asn Ser 45 ta tgc aac agt gct	agaa acctgaggca attagttaaa 120 agaa ataaagc atg cag act Met Gln Thr 1 ttc tac aaa tgg gaa aga 224 Phe Tyr Lys Trp Glu Arg 15 gac tta caa aag aag tgc 272 Asp Leu Gln Lys Lys Cys 30 35 ata ccc att agc ttg gca 320 Ile Pro Ile Ser Leu Ala

		Ser	tcg Ser					tata	ıcat	catg	rctct	tc a	atta	aaa		465
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gcg	gccc	ggc	ctcg	gggc	ag c	Me				n Gl					g att u Ile 10	112
			tgt Cys													160
			att Ile 30													208
			ggc Gly													256
gaa Glu	ttt Phe 60	gag Glu	gct Ala	att Ile	aaa Lys	aat Asn 65	aaa Lys	caa Gln	gat Asp	gta Val	tca Ser 70	ctt Leu	tgt Cys	tct Ser	cta Leu	304
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gct Ala	att Ile	ctg Leu	gaa Glu	tca Ser 95	gat Asp	gcc Ala	aga Arg	gtg Val	aag Lys 100	gaa Glu	caa Gln	cgt Arg	aaa Lys	gga Gly 105	gct Ala	400
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cgc Arg	cat His	gat Asp 125	aaa Lys	gca Ala	agg Arg	gaa Glu	tat Tyr 130	att Ile	gac Asp	aga Arg	atg Met	atc Ile 135	aaa Lys	ata Ile	tca Ser	496

gat ggt agt aaa cag gga cac gtt ttg aaa gca tgg ctt gat att aca Asp Gly Ser Lys Gln Gly His Val Leu Lys Ala Trp Leu Asp Ile Thr 140 145 150	544
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gga ctc caa gat ggg aat gat act ttt gct ctg ctg ggt aag gca caa Gly Leu Gln Asp Gly Asn Asp Thr Phe Ala Leu Leu Gly Lys Ala Gln 175 180 185	640
tgc ctt gag atg cgc cag aat tat tca ggt gcc ctg gag act gtg aac Cys Leu Glu Met Arg Gln Asn Tyr Ser Gly Ala Leu Glu Thr Val Asn 190 195 200	688
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gca aaa ggt tgc tgc tcc aag ata gcc aaa atg tgg aag cac tga gaa Ala Lys Gly Cys Cys Ser Lys Ile Ala Lys Met Trp Lys His * 235 240 245	832
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ttacactcgc cttcagcaga acttgtggac gtagtcaact tattcttcaa aaaattcaaa	1012
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<220>

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Met Val Glu

ttg tta att aat gtg Leu Leu Ile Asn Val 5					163
tca ctg ctt tgg tgg Ser Leu Leu Trp Trp 20			Ser Arg Ph		211
gtt tat ttt ttt ctc val Tyr Phe Phe Leu 1					259
ttt cta ttt ttc ttc Phe Leu Phe Phe 55		tga tctcc t * 60	taaaaatga a	tctagagtt	311
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gcctaactga tagttactt	g attcagtgtg	r ctagacactt	aaatagcatc	tatgtctctt	551
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aataatgcaa taaaaactaq	g ttgaggttag	ctgaggctgg	aaatgccttt	ttcatggtaa	731
atgattcact tctatattt	tetttettt	tcttttttt	tctttggttt	tcatcctgga	791
ttcatcccct gatcttaaat	: caaaacgtca	. gatcaatgaa	ctatgaacta	aagtatttt	851
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ccagggctct gggtcacact ccagg atg act tct cgg aac cag ctg gtg cag 172

aag gtg ctg cag gag ctg cag gaa gca gtg gag tgc gaa ggc ctg gag
Lys Val Leu Gln Glu Leu Gln Glu Ala Val Glu Cys Glu Gly Leu Glu
10 20 25

Met Thr Ser Arg Asn Gln Leu Val Gln

ggt ctc ata ggt gct tcc ttg gag gcc aag cag gtc ctg tct tcc ttc 268
Gly Leu Ile Gly Ala Ser Leu Glu Ala Lys Gln Val Leu Ser Ser Phe
30 35 40

act ctc ccc acc tgc cgg gag gga ggc cct ggc ctc cag gtg ctg gaa 316
Thr Leu Pro Thr Cys Arg Glu Gly Gly Pro Gly Leu Gln Val Leu Glu
45 50 55

gtg gac tcg gtg gcc ctg agc ctg tat cca gaa gat gct cca cgg aac
Val Asp Ser Val Ala Leu Ser Leu Tyr Pro Glu Asp Ala Pro Arg Asn
60 65 70

		tgc Cys						412
		tgg Trp 95						460
		gag Glu						508
		aaa Lys						556
		cct Pro						604
		gcc Ala						652
		cac His 175						700
		tac Tyr						748
		cgg Arg						796
		gct Ala						844
		cct Pro						892
		gcc Ala 255						940
		ctg Leu						988
		gag Glu						1036

	tgg Trp															1084
	tcc Ser 315															1132
	cca Pro															1180
	tac Tyr															1228
gcc Ala	ttg Leu	ccc Pro	ccc Pro 365	agg Arg	gag Glu	gtg Val	ctg Leu	ggc Gly 370	atg Met	gag Glu	gag Glu	cta Leu	gag Glu 375	aag Lys	ctg Leu	1276
	gag Glu															1324
	tca Ser 395															1372
	cat His															1420
	agg Arg															1468
	gcc Ala															1516
	gct Ala															1564
	tgg Trp 475															1612
	cct Pro															1660
	tgg Trp		Arg													1708
ggg	cat	ctc	cct	ttc	tgc	cgc	ttc	cgc	ctc	cgc	tac	ccc	agc	ctg	tca	1756

Gly His Leu Pro Phe Cys Arg Phe Arg Leu Arg Tyr Pro Ser Leu Ser 525 530 535	
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Met Gly Ala Thr Gly Ala Ala Glu

1 5

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Pro Leu Gln Ser Val Leu Trp Val Lys Gln Gln Arg Cys Ala Val Ser

10 15 20

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Leu Glu Pro Ala Arg Ala Leu Leu Arg Trp Trp Arg Ser Pro Gly Pro
25 30 35 40

gga gcc ggc gcc ccc ggc gcg gat gcc tgc tct gtg cct gta tct gag

Gly Ala Gly Ala Pro Gly Ala Asp Ala Cys Ser Val Pro Val Ser Glu

257

45	50	55

					_	aca Thr		_							•	305
						gaa Glu										353
						cac His 95										401
						ctg Leu										449
						acg Thr				-			-	-		497
						aaa Lys										545
						acc Thr										593
						cag Gln 175										641
				gac Asp		tga *	gt a	agco	gtct	t to	atcg	rccat	caa	igtec	att	694
gtta	atga	aa a	agtt	ctac	c ca	cctc	tcag	ttt	tgag	agc	tcct	tttc	ct a	aato	cgccc	754
cccg	rccto	ca c	ccac	gacc	a at	tgta	aaag	taa	acat	gct	tctt	acag	rga a	ıggca	agaaa	814
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ggg gcc agc ccc ggc ttc cta tat tcc gag ggc cag cgg ctg gca ctg Gly Ala Ser Pro Gly Phe Leu Tyr Ser Glu Gly Gln Arg Leu Ala Leu 20 25 30 35	630
gag gct ctg ttg agc aag ggc gcg gag gcg ttc cag acc tgc gtg cag Glu Ala Leu Leu Ser Lys Gly Ala Glu Ala Phe Gln Thr Cys Val Gln 40 45 50	678
cgc gag gag ctg tgg ccc ttc ctc agt gcg gat gag gtt cag ggc ttg Arg Glu Glu Leu Trp Pro Phe Leu Ser Ala Asp Glu Val Gln Gly Leu 55 60 65	726
gca gcg gca gct gaa gac tgg aca gtg gcc aag cag gag ccc agc ggg Ala Ala Ala Glu Asp Trp Thr Val Ala Lys Gln Glu Pro Ser Gly 70 75 80	774
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						ctg Leu										1110
						cag Gln										1158
						gtg Val								-		1206
_		_		_		acc Thr				_			-	_	_	1254
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						gtg Val						-		_	_	1350
						cgg Arg										1398
						aaa Lys							_	-		1446
						gtg Val										1494
						ggc Gly 330					-	_	_	_	_	1542
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gat gct aca Asp Ala Thr			o Arg Gly			26
tgg gcc ccc Trp Ala Pro 470				tga acag gag *	gcccaagc 197	16
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ctgtggtccc a	gctacgcag ga	ıggctgagg t	gggaggatc	cctcgagctc a	aggaggtgga 233	, 6
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180

175

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	tct Ser			-												1949
	gag Glu															1997
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ctg atc aaa ctt g Leu Ile Lys Leu A 40				
agt ctg act gag a Ser Leu Thr Glu T 55				
gga ttc cta gag c Gly Phe Leu Glu L 70				
acc tgg ctg gcc c Thr Trp Leu Ala L			Gly Ser Phe S	
tcc cag cct att g Ser Gln Pro Ile G 105	Sly Met Thr Lys I			
ctg gct gac cag a Leu Ala Asp Gln A 120				
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tgtaaatggc	cagagatgta	tggctggtga		c ctg tgt go Leu Cys Gl		231

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cag cca cct ctg cga gtc cca cag ctg gaa gga gca ccc agt cct Gln Pro Pro Leu Arg Val Pro Gln Leu Glu Gly Ala Pro Ser Pro 25	
aca cta gcc gga cag gcc cgc agc ctg cac tac tga gctg tcacgga Thr Leu Ala Gly Gln Ala Arg Ser Leu His Tyr * 40 45 50	agga 377
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gcctcccttc taaggtcctg tcccactggg cacaggaggc agatccagca gcgtg	ggaatc 240
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-	-	-		_		agc Ser			_	-			_	-		865
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_		_				ttc Phe										961
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	~				_	atc Ile	_			_	-		_	-		1105
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					_	tcg Ser 340	_		_	-	-	_			-	1297
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ctg ctg ctg ccc acg ccc ctg ctg cgg gac ctg tac acc ctg agt gga Leu Leu Leu Pro Thr Pro Leu Leu Arg Asp Leu Tyr Thr Leu Ser Gly 415 420 425	1537									
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	360									

					gag Glu											459
					aag Lys											507
					ccg Pro											555
	_				tgc Cys 65		_	_		_	_			-	-	603
					cac His											651
					Gly gag											699
					cac His											747
					tcg Ser											795
					aag Lys 145											843
					aac Asn											891
	_	_			tgc Cys	_	_	_		_	_				~	939
_	_	_		_	cac His	_	_	_		_						987
_	_	_	_	_	ggc Gly	_	_		_	_	_	_		_	_	1035
_			-		cac His 225	_			_	_		-	-	-		1083

tgt ggc cgt cgc ttc ggc cac cgc tcc aac ctg gcg gag cac gcg cgc Cys Gly Arg Arg Phe Gly His Arg Ser Asn Leu Ala Glu His Ala Arg 240 245 250	1131
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cct ggc gcc acg gcc gcc act gcc acc gag cgt tgc ccg gag tgt gag Pro Gly Ala Thr Ala Ala Thr Ala Thr Glu Arg Cys Pro Glu Cys Glu 300 305 310 315	1323
ggc agc tga gtcccgc agggctgcgg aggggcgcgc tggggcttcg acctggctgc Gly Ser *	1379
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cccggctgcc ctggaactgg gagacaggga gaatcccctg ccggggtccc tggaaacagt	1499
gcccacccca catcactaca ttccctcggc ccgtgttagt gaataaagta ttatatcctc	1559
accccacccg tgcctgtgag tgaggtgggt gggagaggaa gaaagttggg gttctccagg	1619
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cggcacctcg gtttgtgttg gttggaggtg atcgcacact tggcccttgg ttacgtcctc	1739
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ttc agg cat ggc gac ccg cct gag cca cct cca ggg gca aga gat gag Phe Arg His Gly Asp Pro Pro Glu Pro Pro Pro Gly Ala Arg Asp Glu 10 15 20	162								
cag att tac ttt aga aag gac aac agc atc agc cac tgc cac agc ccc Gln Ile Tyr Phe Arg Lys Asp Asn Ser Ile Ser His Cys His Ser Pro 25 30 35	210								
ccc cag atc atc tgt act ggc tgt cag aac agt cct gct gaa acg cca Pro Gln Ile Ile Cys Thr Gly Cys Gln Asn Ser Pro Ala Glu Thr Pro 40 45 50	258								
atc aca cct gtc att cac tgc tct gcc cag gac tct tca gtg ggc tcc Ile Thr Pro Val Ile His Cys Ser Ala Gln Asp Ser Ser Val Gly Ser 55 60 65 70	306								
cca gcg cta agc att tgg cct gac act cca ggc gcc atg tgc cct ggt Pro Ala Leu Ser Ile Trp Pro Asp Thr Pro Gly Ala Met Cys Pro Gly 75 80 85	354								
ccc cac cta cct ctc cac tgc aaa ttc tgg cca tac acc cct gca ccc Pro His Leu Pro Leu His Cys Lys Phe Trp Pro Tyr Thr Pro Ala Pro 90 95 100	402								
cca aac agt gca ctc cca tct cag tcc aca ttc tcc cct tac aac atg Pro Asn Ser Ala Leu Pro Ser Gln Ser Thr Phe Ser Pro Tyr Asn Met 105 110 115	450								
att cat cca aga cca tgg att cgt ggc ctt aag ttt act tct ggt ctg Ile His Pro Arg Pro Trp Ile Arg Gly Leu Lys Phe Thr Ser Gly Leu 120 125 130	498								
gac ttc tgt gtc agc tcc aga gta tag ttgtc tcactgaccc cttcacttgg Asp Phe Cys Val Ser Ser Arg Val * 135 140	550								
gtgccagaga acactggata ttccagaccc c	581								

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                                                                        53
                                              Met Gly Leu Gly Pro
cct acc gac ggc cca gga ccc atc gac cca cga gtc ggt ccg gcc gcc
                                                                       101
Pro Thr Asp Gly Pro Gly Pro Ile Asp Pro Arg Val Gly Pro Ala Ala
                                                          20
                 10
                                      15
                                                                      149
ggg tgc aca atg ggt ggc tcc tcc agc gtc gcc gct atg aag aaa gtg
Gly Cys Thr Met Gly Gly Ser Ser Ser Val Ala Ala Met Lys Lys Val
             25
                                  30
gtt caa cag ctc cgg ctg gag gcc gga ctc aac cgc gta aaa gtt tcc
                                                                      197
Val Gln Gln Leu Arg Leu Glu Ala Gly Leu Asn Arg Val Lys Val Ser
                             45
cag gca gct gca gac ttg aaa cag ttc tgt ctg cag aat gct caa cat
                                                                      245
Gln Ala Ala Ala Asp Leu Lys Gln Phe Cys Leu Gln Asn Ala Gln His
                                                                      293
gac cct ctg ctg act gga gta tct tca agt aca aat ccc ttc aga ccc
Asp Pro Leu Leu Thr Gly Val Ser Ser Ser Thr Asn Pro Phe Arg Pro
                     75
70
                                          80
                                                                      317
cag aaa gtc tgt tcc ttt ttg tag
Gln Lys Val Cys Ser Phe Leu *
                 90
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	180		18	35		190	

_	e Gln Phe S			gtg cga ctg ccc tgc Val Arg Leu Pro Cys 205	862
				gtg cag gag cta ggc Val Gln Glu Leu Gly 220	910
	Gly Ile T		-	att caa ggc tct cat Ile Gln Gly Ser His 240	958
taa agac at *	tttagtag t	cctgaccct	agtatttctg t	gggcaagga gagggctgaa	1015
gaactgtctt	tgcaagctat	. ctggctgca	a agtgagaatt	tgagtcctgg cttccacatt	1075
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tataacgagc	ttcataaacc	: tcgatgaga	t atttgagggg	gagggaacaa tacttaccct	1435
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ttgaagatcg tgacgtcttg taactagcag tgtgtgcaca gaatcctact caaggaacgt 180
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aatagtatag aagaattcaa gagaggagag agagacagca ccgaatgaag actgtaaaag 300

aaaagaagga atgccagaga ttgagaaaat ctgccaagac taggagggta acccagagga	360
aaccgtcttc agggcctgtt tgctggct atg ctt cga gaa cct ggg gat ccc Met Leu Arg Glu Pro Gly Asp Pro 1 5	412
gaa aaa tta ggg gaa ttt ctt cag aaa gac aat atc agc gtg cat tat Glu Lys Leu Gly Glu Phe Leu Gln Lys Asp Asn Ile Ser Val His Tyr 10 15 20	460
ttc tgt ctt atc tta tct agt aag ctg cct cag agg ggc cag tcc aac Phe Cys Leu Ile Leu Ser Ser Lys Leu Pro Gln Arg Gly Gln Ser Asn 25 30 35 40	508
aga ggt ttc cat gga ttt ctg cct gaa gac atc aaa aag gag gca gcc Arg Gly Phe His Gly Phe Leu Pro Glu Asp Ile Lys Lys Glu Ala Ala 45 50 55	556
cgg gct tct agg aag atc tgc ttt gtg tgc aag aaa aag gga gct gct Arg Ala Ser Arg Lys Ile Cys Phe Val Cys Lys Lys Lys Gly Ala Ala 60 65 70	604
atc aac tgc cag aag gat cag tgc ctc aga aac ttc cat ctg cct tgt Ile Asn Cys Gln Lys Asp Gln Cys Leu Arg Asn Phe His Leu Pro Cys 75 80 85	652
ggc caa gaa agg ggt tgc ctt tca caa ttt ttt gga gag tac aaa tca Gly Gln Glu Arg Gly Cys Leu Ser Gln Phe Phe Gly Glu Tyr Lys Ser 90 95 100	700
ttt tgt gac aaa cat cgc cca aca cag aac atc caa cat ggg cat gtg Phe Cys Asp Lys His Arg Pro Thr Gln Asn Ile Gln His Gly His Val 105 110 115 120	748
ggg gag gaa agc tgc atc tta tgt tgt gaa gac tta tcc caa cag agt Gly Glu Glu Ser Cys Ile Leu Cys Cys Glu Asp Leu Ser Gln Gln Ser 125 130 135	796
gtt gag aac atc cag agc ccg tgt tgt agt caa gcc atc tac cac cgc Val Glu Asn Ile Gln Ser Pro Cys Cys Ser Gln Ala Ile Tyr His Arg 140 145 150	844
aag tgc ata cag aaa tat gcc cac aca tca gca aag cat ttc ttc aaa Lys Cys Ile Gln Lys Tyr Ala His Thr Ser Ala Lys His Phe Phe Lys 155 160 165	892
tgt cca cag tgt aac aat cga aaa gag ttt cct caa gaa atg ctg aga Cys Pro Gln Cys Asn Asn Arg Lys Glu Phe Pro Gln Glu Met Leu Arg 170 175 180	940
atg gga att cat att cca gac agg agg tgg tgc ctc att ctg tgt gct Met Gly Ile His Ile Pro Asp Arg Arg Trp Cys Leu Ile Leu Cys Ala 185 190 195 200	988
act gcg gat ccc acg gaa ccc aca gga ctg ctc ctc tct tag atctaac Thr Ala Asp Pro Thr Glu Pro Thr Gly Leu Leu Ser * 205 210	1037

1097 agtaagaaat gggagtgtga ggagtgttca cctgctgcag ccacagacta catacctgaa aactcagggg acatcccttg ctgcagcagc accttccacc ctgaggaaca tttctgcaga 1157 gacaacacct tggaagagaa tccgggcctt tcttggactg attggccaga accttcctta 1217 1277 ttagaaaagc cagagtcctc tcgtggcagg aggagctact cctggaggtc caagggtgtc agaatcacta acagctgcaa aaaatccaag taacaccttc tgagtagctg ctgtcccaca 1337 1397 caatagggta tgaagctgcg ctcctccatc gggtttgggg agggagcact ctgggactgt 1457 qaqacaaqqa agcaqggcca gcagtgagac tatgagccaa gcaaagagaa gtctcagtgg agcatgagga gggagcagtc cagatgccaa caaggaaatg cgtttatggc tacaagagtg 1517 1577 cctctgcttt ctcctcctct cctcccacca aggattcttc caccttaatc ttgttttcat atgcctcttc ttacttcacc catgtttgtt gttatgcaaa taaaggtttt ctctccaaaa 1637 1645 aaaaaaaa

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tgc tac tgt ggt gca gtg gca aag aga caa gag aaa aaa ggg atg gag

366

Cys Tyr Cys Gly Ala Val Ala Lys Arg Gln Glu Lys Lys Gly Met Glu 55 60 65	
cct ctt caa ggt cat gcc act ccc gct ttg cct ttt aaa gaa acc cag Pro Leu Gln Gly His Ala Thr Pro Ala Leu Pro Phe Lys Glu Thr Gln 70 75 80	414
gaa cta tta cta agt ccc ctg ccc cag gaa ggt cct ggg tca ctt gca Glu Leu Leu Ser Pro Leu Pro Gln Glu Gly Pro Gly Ser Leu Ala 85 90 95	462
gca gga gag agc agc agt ctt tct gcc agt aca tca gtc tca gat tca Ala Gly Glu Ser Ser Ser Leu Ser Ala Ser Thr Ser Val Ser Asp Ser 100 105 110 115	510
tcc cag aaa aaa gaa gag cac aat tat tct ctt ttt gtc tcc gac aac Ser Gln Lys Lys Glu Glu His Asn Tyr Ser Leu Phe Val Ser Asp Asn 120 125 130	558
ttg ggt gaa cag cca act aaa tgc agt cct gaa gaa gat gag gag gac Leu Gly Glu Gln Pro Thr Lys Cys Ser Pro Glu Glu Asp Glu Glu Asp 135 140 145	606
gag gag gat gtt gat gat gag gac cat gat gaa gga ttc ggc agt gag Glu Glu Asp Val Asp Asp Glu Asp His Asp Glu Gly Phe Gly Ser Glu 150 155 160	654
cat tac atc att ata taa tggtacttcc tcaagttgct gg His Tyr Ile Ile * 165	694
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420 cggcctgtgg gaatgagtca ggcttctcct gatctggcgc tcaggaggtc tctgattctg 480 qtqttqqcct ccctccttgc cggtgccatt actgtcactt gtctttcatc tgggaaggcg 540 attggcactg acctaggect tgcctcatta gccagcaatg ctggctaatg acccatttac aaccatcacc aaacatcacc tattcagcca ttaaccaccg tgcatcttta ccccttgatt 600 cttgttactg cccaccacc attatcagtg ttaatgaact tcaccatcac tgccttcttg 660 720 aattaatttt cattatcttg cctcttcact ggtttttaat gtgcatgccc ttcactatct ctgccagcct ccattcattc ccacgattga gcattccccg ccactttgta acctgtctcc 780 840 attctccatg atccctcacc tgtttcagca ccactgaata ttgtcactaa cttggaagcc 900 agccqcaccc tqcatqqqqa agtcccctct ctgqagtcca gcaagtccca gtgacagaac 960 ccataccatt tccccagata gctttgctcc tcgttcattt tggcctttct ccctttggtt gggggccatt tgcctctccc ttctcccctg ctgtgccttt cctctcagtt tattgaccag 1020 atg cct gta tta agg gcc gag gtg gaa gag ctc caa 1068 tttgaggaga ac Met Pro Val Leu Arg Ala Glu Val Glu Glu Leu Gln 1 5 gcc cag acc cgg gaa ccc cga gag gtc ata ttt gag gat gtt ctg ctt 1116 Ala Gln Thr Arg Glu Pro Arg Glu Val Ile Phe Glu Asp Val Leu Leu cgg aga ccc aag tgc acc cca gac atg gat gtc atc ctc aac att cct 1164 Arg Arg Pro Lys Cys Thr Pro Asp Met Asp Val Ile Leu Asn Ile Pro 1218 Val Glu Glu Pro Leu Pro Phe * 45 50 tgctctcttc ccagcacctg gagccttgga tcatttactt ccaggaccgg atctccattc 1278 1338 agaccetgat ctacagtete cetgetecet etgecettee tecetette tttecetece 1398 teceteettt etttetteet gtggtttttt cetetettet tecettettt etggttggtg 1458 ctgctgggcc aggtgggaat ttctgattaa atctgctatt ccttttttac caataaagct 1518

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1540

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60

120

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gct gtg gaa agt aag cca agt cgt aag agc gta tgc atc aac cct ctg Ala Val Glu Ser Lys Pro Ser Arg Lys Ser Val Cys Ile Asn Pro Leu 10 15 20	222
atg tcc ccc aag ctt gcc ctg caa gtg gat gca gat ggg ttt cct gtt Met Ser Pro Lys Leu Ala Leu Gln Val Asp Ala Asp Gly Phe Pro Val 25 30 35	270
aag ccc aag agt act gaa gga atg aag gga agg aag ggg aag cag gtg Lys Pro Lys Ser Thr Glu Gly Met Lys Gly Arg Lys Gly Lys Gln Val 40 45 50 55	318
tct gaa atc ttg cct aaa gca gaa gtt cag agt aaa cgc aag aga aca Ser Glu Ile Leu Pro Lys Ala Glu Val Gln Ser Lys Arg Lys Arg Thr 60 65 70	366
gaa ggc agc cct cca gat agt aag aac aag ggg cct acg gtg aaa Glu Gly Ser Ser Pro Pro Asp Ser Lys Asn Lys Gly Pro Thr Val Lys 75 80 85	414
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aag agg cca gct gca agg gac aga agc agc caa ccc ccc aaa aag acg Lys Arg Pro Ala Ala Arg Asp Arg Ser Ser Gln Pro Pro Lys Lys Thr 105 110 115	510
tct ttg aaa gag aat aaa gtg aag atc cct aaa aag tcc gct ggg aag Ser Leu Lys Glu Asn Lys Val Lys Ile Pro Lys Lys Ser Ala Gly Lys 120 125 130 135	558
agc tgc cct ccc tcc agg aaa gaa aaa gag aat aca aac aaa agg cct Ser Cys Pro Pro Ser Arg Lys Glu Lys Glu Asn Thr Asn Lys Arg Pro 140 145 150	606
tcc cag tct att gcc tcg gaa aca ctg acg aaa cct gca aaa cag aag Ser Gln Ser Ile Ala Ser Glu Thr Leu Thr Lys Pro Ala Lys Gln Lys 155 160 165	654
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cag agt agt gga aag act cgg gcc aga ccc tca acg aaa acc cca gag Gln Ser Ser Gly Lys Thr Arg Ala Arg Pro Ser Thr Lys Thr Pro Glu 185 190 195	750
agc agt gca gct cag aga aag cga aag ctg aag gca aag ctg gac tgt Ser Ser Ala Ala Gln Arg Lys Arg Lys Leu Lys Ala Lys Leu Asp Cys 200 205 210 215	798
tcg cac ggc aaa cgg agg cgg ctg gat gca aag tga ttgg aaagatggta	848

Ser His Gly Lys Arg Arg Arg Leu Asp Ala Lys * 220 225

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gac gcc gtg gat gcc acc atg gag aaa ctc cgg gca cag tgc ctg tcc Asp Ala Val Asp Ala Thr Met Glu Lys Leu Arg Ala Gln Cys Leu Ser 5 10 15	166										
cgc ggg gcc tcg ggc atc cag ggc ctg gcc agg ttt ttc cgc caa cta Arg Gly Ala Ser Gly Ile Gln Gly Leu Ala Arg Phe Phe Arg Gln Leu 20 25 30	214										
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ctg gcc aaa ctc ggg ctg gtg ctg gac cag gcg gag gca gag ggt gtg Leu Ala Lys Leu Gly Leu Val Leu Asp Gln Ala Glu Ala Glu Gly Val 50 55 60 65	310										
tgc agg aag tgg gac cgc aat ggc agc ggg acg ctg gat ctg gag gag Cys Arg Lys Trp Asp Arg Asn Gly Ser Gly Thr Leu Asp Leu Glu Glu 70 75 80	358										
ttc ctt cgg gcg ctg cgg ccc ccc atg tcc cag gcc cgg gag gct gtc Phe Leu Arg Ala Leu Arg Pro Pro Met Ser Gln Ala Arg Glu Ala Val 85 90 95	406										
atc gca gct gca ttt gcc aag ctg gac cgc agt ggg gac ggc gtc gtg Ile Ala Ala Ala Phe Ala Lys Leu Asp Arg Ser Gly Asp Gly Val Val 100 105 110	454										
acg gtg gac gac ctc cgc ggg gtg tac agt ggc cgt gcc cac ccc aag Thr Val Asp Asp Leu Arg Gly Val Tyr Ser Gly Arg Ala His Pro Lys 115 120 125	502										
gtg cgc agt ggg gag tgg acc gag gac gag gtg ctg cgc cgc ttc ctg Val Arg Ser Gly Glu Trp Thr Glu Asp Glu Val Leu Arg Arg Phe Leu 130 135 140 145	550										
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tgc agg aag tgg gac cgc aat ggc agc ggg acg ctg gat ctg gag gag

Cys Arg Lys Trp Asp Arg Asn Gly Ser Gly Thr Leu Asp Leu Glu Glu

70

75

80

ttc ctt cgg gcg ctg cgg ccc ccc atg tcc cag gcc cgg gag gct gtc

Phe Leu Arg Ala Leu Arg Pro Pro Met Ser Gln Ala Arg Glu Ala Val

85

90

95

atc gca gct gca ttt gcc aag ctg gac cgc agt ggg gac ggc gtc gtg Ile Ala Ala Phe Ala Lys Leu Asp Arg Ser Gly Asp Gly Val Val 100 105 110	454
acg gtg gac gac ctc cgc ggg gtg tac agt ggc cgt gcc cac ccc aag Thr Val Asp Asp Leu Arg Gly Val Tyr Ser Gly Arg Ala His Pro Lys 115 120 125	502
gtc aca ctg gcg gaa ttc cag gac tac tac agc ggc gtg agt gcc tcc Val Thr Leu Ala Glu Phe Gln Asp Tyr Tyr Ser Gly Val Ser Ala Ser 130 135 140 145	550
atg aac acg gat gag gag ttc gtg gcc atg atg acc agt gcc tgg cag Met Asn Thr Asp Glu Glu Phe Val Ala Met Met Thr Ser Ala Trp Gln 150 155 160	598
ctg tga gcagctccgg ctcagccctg ctgccctggc ctgtcactcc ccacccctgc Leu *	654
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Met Val Arg

1

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tgc gga ccc cag att cgt ccc cct cca cca cac aca acg cca aga cgg Cys Gly Pro Gln Ile Arg Pro Pro Pro Pro His Thr Thr Pro Arg Arg 20 25 30 35	273
gcc cca gga ggg cgt gaa gag aag act tcc ttt cct ctc ctc tcg cct Ala Pro Gly Gly Arg Glu Glu Lys Thr Ser Phe Pro Leu Leu Ser Pro 40 45 50	321
cct ggc gct ggc cgt atg aag gtg tct ccc aga agc att agc aga gga Pro Gly Ala Gly Arg Met Lys Val Ser Pro Arg Ser Ile Ser Arg Gly 55 60 65	369
gcc ctg tgg gag aaa tga ggagtg acccaaaaga aacttgctca aggacagcct Ala Leu Trp Glu Lys * 70	423
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ctg ggg ggt gac gag gag aag gac cca gac gcc gcc aag aag	272

320 qaq cqq caq qaq qcq ctq cqc caq qcq gag gag gag cgc aag gcc aag Glu Arg Gln Glu Ala Leu Arg Gln Ala Glu Glu Glu Arg Lys Ala Lys 368 tac gcc aag atg gag gcg gag cgc gag gcc gtg cgc cag ggc atc cga Tyr Ala Lys Met Glu Ala Glu Arg Glu Ala Val Arg Gln Gly Ile Arg 65 55 416 gac aag tac ggc atc aag aag gag gag cgc gag gcc gag gcc cag Asp Lys Tyr Gly Ile Lys Lys Glu Glu Arg Glu Ala Glu Ala Gln 70 75 gcc gcc atg gag gcc aac tcc gag ggg agc ttg acg cgg ccc aag aag 464 Ala Ala Met Glu Ala Asn Ser Glu Gly Ser Leu Thr Arg Pro Lys Lys 512 qcc atc ccq ccq ggc tqc ggg gac gag gtg gag gag gac gag agc Ala Ile Pro Pro Gly Cys Gly Asp Glu Val Glu Glu Asp Glu Ser 105 110 100 560 atc ctq qac acc gtc atc aag tac ctg ccc ggg ccg ctg cat gac atg Ile Leu Asp Thr Val Ile Lys Tyr Leu Pro Gly Pro Leu His Asp Met 120 125 ctc aag atg tat ccc cgc gcg gga cag ctg ccc cgc gga gcc ggc cat 608 Leu Lys Met Tyr Pro Arg Ala Gly Gln Leu Pro Arg Gly Ala Gly His 140 135 665 tga acac tgcaccctcc acaggagccg cagaggccct gaggcaccgg actgcttgga gaccetgege ecetgeecag caceteetee gtgggeaget ceteggtgtg gggeetgegg 725 785 ggttccctgc ggcgcagccg ggcgcgtgtg tggcctaatc cacctggtgg ccctgcgggg 845 cggcatccga gccctgttt ctcctccatt catgtttatt ttgcatcaca atttgttgaa 905 tctcaggtag atgaggtctt tgcatttagt gagttttatc ttgacagggc gcgctcgccc 965 ccggtccctt tcgtccacat caaaaatgca tcacgtctcc acgtgtttcg ggccagggcg qqqcttqqca ttqaccttca tgaccttaca tagctttaga gaagccataa cgcttgactg 1025 caatactaac gaccgacgcc cctccggaca gagaccaccg cgcccctctg cgccccatcg 1085 acgctgtccg cggngacgtc gctgaccgcc ctgctcgccc tgagccctct cactgacttc 1145 1170 tcccgggtcg tgtcttatta aaact

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ctcggcctct tgcttgagag acagattgga gcagagtctt tgtggatgca aagccacctg	180
ggccactgcc gtgtgtgcca ccctgaactt caagctgccc tgaaccgcgt gcgtttctca	240
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acttgagtag acaagc atg aga ata tca tta ttt tta tat gtt ata tgt Met Arg Ile Ser Leu Phe Leu Tyr Val Ile Cys 1 5 10	529
tat att ttt agc aga gaa aaa agt gga aaa tgt gtg caa act tgc aga Tyr Ile Phe Ser Arg Glu Lys Ser Gly Lys Cys Val Gln Thr Cys Arg 15 20 25	577
agg ccc ccc gga gga ggg tcg tcc ctg tgc cca tgc tgt cag gaa ggc Arg Pro Pro Gly Gly Gly Ser Ser Leu Cys Pro Cys Cys Gln Glu Gly 30 35 40	625
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										cat His				98
										gcc Ala			:	146
				-		_				cag Gln				194
										ctc Leu			:	242
	-				_					gtt Val 90			:	290
										gtt Val			:	338
										caa Gln			:	386
										tgg Trp				434
										gct Ala				482
										gaa Glu			!	530

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2012

2072

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Met Leu Glu Ala Gly Gly Ser Glu Ala Ala Thr Ala Arg Gly Arg Gly
50 55 60

gac ttt gga gct gcc tca tgc agc gac ctc gcc ttc cgc tgc gcc tcc

Asp Phe Gly Ala Ala Ser Cys Ser Asp Leu Ala Phe Arg Cys Ala Ser

65 70 75

tcc cag aac cca aga agc ctg gaa cct gtg gcg tcc agc cct gaa agg
Ser Gln Asn Pro Arg Ser Leu Glu Pro Val Ala Ser Ser Pro Glu Arg
80 85 90 95

396 agg aga cgg caa ccc agc cgc gct ttt gcc tgc act ctc cct gga tgc Arg Arg Arg Gln Pro Ser Arg Ala Phe Ala Cys Thr Leu Pro Gly Cys 100 105 tqq aqq ctq gaq gca gtg acg cag caa cag cgc gag gcg act ttg gag 444 Trp Arg Leu Glu Ala Val Thr Gln Gln Gln Arg Glu Ala Thr Leu Glu 125 115 120 cgg cct cat ata gcg acc tcg cct tcc gct gcg cgt cct ccc aga gcc 492 Arg Pro His Ile Ala Thr Ser Pro Ser Ala Ala Arg Pro Pro Arg Ala 130 135 540 caa gaa gcc cgg aac ctg tgg cat cca tct ctg aaa gga gaa gac ggc Gln Glu Ala Arg Asn Leu Trp His Pro Ser Leu Lys Gly Glu Asp Gly 150 588 aac cca gcc gag gca cta ctg ggt tgg ggt ctc cac gac cga gct ggt Asn Pro Ala Glu Ala Leu Leu Gly Trp Gly Leu His Asp Arg Ala Gly 165 637 ctc atc aag tgg cgt cca aca agg ggc tca aac ccg ggt tga ggggttg Leu Ile Lys Trp Arg Pro Thr Arg Gly Ser Asn Pro Gly 180 185 ctggagcgac ggagaacgtg gaactacact ggaggacacc agagtactct taagcaatcc 697 cttggccaaa accagcaact gatttggata ccatcaagac acctgaaatc ttgtcatgag 757 ccagatactg aggaagagat tttgggaaga acccaaggac ccccagttg cagccatgtc 817 aagactgaca ataaggaaga catcagtccc agcaagcaac attcatcggg cacagccacc 877 catgtggggc cagatcaaga agttgacaca gacggcggaa gaaaatctga agaaagcgga 937 997 tgaccagcta caatgagtaa tctaatggta gctatgatgg ctgtgctcac cattgccatg agtattcccc cagcacctgc tgaaacaaaa aacattatac ttattgggca tatattcctt 1057 1117 ttccaccagt ttcatggcca gtgacatggt tagacccccc agtggaggta tacactaatg atagettttq gatacetggt tetacagatg atagaggeec ateteacece caaaaggagg 1177 1204

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782

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gtg	aatg	aca	tggg	agac	ag a	cctg	gggt	c tt	ttag	ggac	gga	aagc	ctc	agcc	aagacc	120
cag	actc	cca	gggt	catc	aa c	ctcc	tcgg	g tc	acta	accc	tcc	ccag	tgt	ctgt	ctaccc	180
cta	agtc	cag .	agaa	cacg	tc c	tctc	tagg	c tc	gagc	cgga	atc	aata	tag	gcta	caaggg	240
cat	cagt	tca	ggct	gcgc	gg a	ggag	agaa	g ga	agtg	ctga	tgt	ggag	tcc	tccc	tccccc	300
atg	gca	tca	cccc gag Glu	gca	gaa	aaa	aca	ttc	cat	cgg	ttt	gct	aca	ttt	cc gga Gly	356 404
gaa Glu	tca Ser	tca Ser	agc Ser 20	agt Ser	ggc Gly	act Thr	gaa Glu	atg Met 25	aac Asn	aac Asn	aag Lys	aac Asn	ttc Phe 30	tcc Ser	aag Lys	452
ctg Leu	tgc Cys	aaa Lys 35	gac Asp	tgt Cys	ggc Gly	atc Ile	atg Met 40	gat Asp	ggc Gly	aag Lys	aca Thr	gtc Val 45	acc Thr	tcc Ser	acg Thr	500
gac Asp	gtg Val 50	gac Asp	atc Ile	gtg Val	ttc Phe	agc Ser 55	aaa Lys	gtc Val	aag Lys	gcc Ala	aag Lys 60	aac Asn	gcc Ala	cga Arg	acc Thr	548
atc Ile 65	acg Thr	ttt Phe	caa Gln	cag Gln	ttc Phe 70	aaa Lys	gag Glu	gca Ala	gtg Val	aag Lys 75	gaa Glu	ctg Leu	ggc Gly	cag Gln	aag Lys 80	596
cgc Arg	ttc Phe	aaa Lys	ggg Gly	aag Lys 85	agt Ser	cca Pro	gat Asp	gaa Glu	gtc Val 90	ctg Leu	gag Glu	aac Asn	att Ile	tat Tyr 95	gga Gly	644
ctc Leu	atg Met	gag Glu	ggc ggc	aaa Lys	gac Asp	cca Pro	gcc Ala	acc Thr	act Thr	ggc Gly	gct Ala	act Thr	ttt Phe	ccc Pro	tgg Trp	692

100	105	110

tta cct atg caa gaa acc tga aa gtgatcctag acccctccac ctccccaatc Leu Pro Met Gln Glu Thr * 115	745
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ccaggaattg aatcctgcct ctgcagctta caaactgcac accatctatc tgtttacgaa	865
accactgaaa gcttccttgt ttcatctgtt catgaggata gtattttta ctcacggcag	925
tatgaggatc cattaagatg tatatcaaga gtttttagac cagtgcccgg cacatgtgga	985
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tca aac tgg tgg cct ctc ggt ctg cag tct tat gct cta acc ctg agc Ser Asn Trp Trp Pro Leu Gly Leu Gln Ser Tyr Ala Leu Thr Leu Ser 15 20 25	157
tat acc cct tcc tgc tgc tgt ggg ggt caa tta atg cct ttg act tgt Tyr Thr Pro Ser Cys Cys Cys Gly Gly Gln Leu Met Pro Leu Thr Cys 30 35 40	205
gcg gtc aca ccc aga tga ccagtc acctgtgtgt tgccacttca caatggaagc Ala Val Thr Pro Arg * 45 50	259
tcctaggagc tgccaggtct acctcagtga aaactcattg accttgtgca tagcaagagg	319
cagtccccgc tcctcagata acccccgtgc ctgtgtcttc cctgccttga gtccttagtt	379
atgggcagca ggctggaaaa gcactgccag cagccactag aatggccttg agagtcatcc	439
tccagtaact gtttatggtg ggcacataca agagaaactt tgtgtgactg aggtgtctgt	499

tetaaaacac ttaatgacag agttgggeet ggeteteetg gteeagtgtt ceatteaggg 559
cagatteage acaactgeag tetaggacaa aagatgatte ttteaacttt taettettea 619
gttaatacaa atgaagaatg ttagagaagg agcaacteea agaaatagtg agaagtgtgt 679
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cgcctgggct gccggacggt gggaacggaa gtcgctgtgg gacgctgagg aagccagg
atg gcg act ccg agc aag aag acg tca act cca agc ccc cag cct tcc
Met Ala Thr Pro Ser Lys Lys Thr Ser Thr Pro Ser Pro Gln Pro Ser
1 5 10 15

aag aga gct ctc ccg aga gac cct tcg tcg gag gtc ccg agc aag agg
Lys Arg Ala Leu Pro Arg Asp Pro Ser Ser Glu Val Pro Ser Lys Arg
20 25 30

aag aat tcg gcc ccg cag ctg ccg ctg ttg cag tcg tcc ggg cct ttc
Lys Asn Ser Ala Pro Gln Leu Pro Leu Leu Gln Ser Ser Gly Pro Phe
35
40
45

gtg gaa ggc tct atc gtc cgc atc tcg atg gag aac ttc cta aca tat
Val Glu Gly Ser Ile Val Arg Ile Ser Met Glu Asn Phe Leu Thr Tyr
50 55 60

gat att tgt gaa gta tct cct gga ccc cac ttg aat atg atc gtt gga
Asp Ile Cys Glu Val Ser Pro Gly Pro His Leu Asn Met Ile Val Gly
65 70 75 80

gcc aat gga aca ggg aag tcg agc att gtg tgt gcc att tgc ctt ggt 406 Ala Asn Gly Thr Gly Lys Ser Ser Ile Val Cys Ala Ile Cys Leu Gly 85 90 95

tta gct gga aaa cct gct ttc atg gga cga gca gat aag gtt ggg ttt
Leu Ala Gly Lys Pro Ala Phe Met Gly Arg Ala Asp Lys Val Gly Phe
100 105 110

ttt gtg aag aga gga tgt tct aga ggc atg gtt gaa att gaa ttg ttc
Phe Val Lys Arg Gly Cys Ser Arg Gly Met Val Glu Ile Glu Leu Phe
115 120 125

agg gct tct gga aat ctt gta atc acc cgt gag att gat gtg gca aaa 550

Arg Ala Ser Gly Asn Leu Val Ile Thr Arg Glu Ile Asp Val Ala Lys 130 135 140	
aat cag tcc ttt tgg ttc atc aac aaa aaa tct aca acc cag aaa ataAsn Gln Ser Phe Trp Phe Ile Asn Lys Lys Ser Thr Thr Gln Lys Ile145150	598
gtg gaa gag aaa gtt gca gcc tta aat att cag tgg gga atc ttt gcc Val Glu Glu Lys Val Ala Ala Leu Asn Ile Gln Trp Gly Ile Phe Ala 165 170 175	646
agt ttc tcc tca gga caa gtt gga gga att tgc taa actc agcaaattgg Ser Phe Ser Ser Gly Gln Val Gly Gly Ile Cys * 180 185	696
actcctcgaa gcactggaaa gttcaatggg cccccagaaa ttgcgcaata tcctgtgtac	756
tccaaactgt ggagaagaag aacagtcccg acccctgcgc agagaaactg ctgtctctcg	816
cgaaatggtg tgcccgcttc gaggattata cccccggtgg gagggcttct agcagggccg	876
cacatattcg agctgccacc cacagcacgc tggacaaaag ctcgcgcctc agagacatat	936
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cct gga gaa gtc ctt att gat tgt tta gat tcc att gaa gac acc aaa Pro Gly Glu Val Leu Ile Asp Cys Leu Asp Ser Ile Glu Asp Thr Lys 30 35 40	146											
gga aat aat gga gat aga ggt aga ctc ttg gta aca aat tta aga att Gly Asn Asn Gly Asp Arg Gly Arg Leu Leu Val Thr Asn Leu Arg Ile 45 50 55	194											
ctc tgg cac tct ttg gca tta tca aga gtc aat gtt tct gtc ggt tac Leu Trp His Ser Leu Ala Leu Ser Arg Val Asn Val Ser Val Gly Tyr 60 65 70	242											
aat tgc ata ttg aat att aca aca agg act gct aac tct aaa tta cga Asn Cys Ile Leu Asn Ile Thr Thr Arg Thr Ala Asn Ser Lys Leu Arg 75 · 80 85	290											
ggc caa act gaa gct ctc tat ata cta aca aaa tgt aac agt act cgt Gly Gln Thr Glu Ala Leu Tyr Ile Leu Thr Lys Cys Asn Ser Thr Arg 90 95 100 105	338											
ttt gaa ttt ata ttt aca aat ttg gtt cct gga agc cct aga ctt ttt Phe Glu Phe Ile Phe Thr Asn Leu Val Pro Gly Ser Pro Arg Leu Phe 110 115 120	386											
act tot gtg atg gca gta cac aga gct tat gaa act tot aaa atg tat Thr Ser Val Met Ala Val His Arg Ala Tyr Glu Thr Ser Lys Met Tyr 125 130 135	434											
cgt gat ttt aaa tta aga agt gca cta att cag aac aag caa cta aga Arg Asp Phe Lys Leu Arg Ser Ala Leu Ile Gln Asn Lys Gln Leu Arg 140 145 150	482											

														tgg Trp		530
tta Leu 170	tcc Ser	agt Ser	gat Asp	cag Gln	ggc Gly 175	aat Asn	tta Leu	gga Gly	acc Thr	ttt Phe 180	ttt Phe	att Ile	acc Thr	aat Asn	gtg Val 185	578
														agt Ser 200		626
														ttt Phe		674
														gtt Val		722
														aag Lys		770
atc Ile 250	aat Asn	tca Ser	ctt Leu	cac His	aaa Lys 255	gtc Val	tat Tyr	tct Ser	gcc Ala	agt Ser 260	ccc Pro	ata Ile	ttt Phe	gga Gly	gtt Val 265	818
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														acg Thr		914
														cgt Arg		962
	_			_	_	_			-					aag Lys		1010
					gga Gly 335							tga *	ttg	acct [.]	tga	1059
gtt	gaga	tgg (attt	ctat	ta aa	agata	atct	c tag	gttta	aaag	ata	ctag	tca (cctg	ccataa	a 1119
gtc	atgga	aat a	agtt [.]	ttta	ta ti	ttaca	agct	t tta	atati	ttaa	aac	ttgt	aag (agtt	ttttta	a 1179
atg	attga	agg (aaaa	agtc	at ti	taga	aaac	t tc	agtti	ttcg	gcc	agcg	cgt	cgag	ggaggg	1239
gcc	agcga	aca (catg	gcct	ag ta	aacc	gtcc	g gc	cgcg	gcgc	tgg	ctta	agc	catg	gctgag	1299

1359 qqtaqccqqa ttcctcaggc ccgggcgctc ctacagcagt gcctgcacgc ccggctgcaa attcgcccag ccgatgggga cgtcgcggcc cagtgggtgg aggtccaaag aggactggtg 1419 1479 atctacqtqt qctttttcaa qqqaqctqat aaaqaacttc ttcccaaaaat qgatctacqa 1539 ctctggctcc actgattacc ttaaccatat tacatggaat gatgtaaggg agaaacagaa qactettqtt gaacagetce tgtetttgtt gaacagetce ecagggeete etaceegeaa 1599 actgcttgct aagaatctag ccatacttta tagtattgga gacacattct ccgttcatga 1659 agcaatcgat aaatgtaatg atcttattcg tagcaaagat gattctccaa gttatcttcc 1719 1771

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cgggtcgacg atttcgttgc gcgttccgga actggtttcc cggaaggatt atgtctgcgc 120

60

cctcgatccg accggaagtt gcacgctgag ccgcggacac c atg cag tcg gat 173

Met Gln Ser Asp

1

gat gtt atc tgg gat aca cta gga aac aag caa ttt tgt tcc ttc aaa 221
Asp Val Ile Trp Asp Thr Leu Gly Asn Lys Gln Phe Cys Ser Phe Lys
5 10 15 20

ata aga acc aag act cag agc ttc tgc cga aat gaa tat agc ctg act

11e Arg Thr Lys Thr Gln Ser Phe Cys Arg Asn Glu Tyr Ser Leu Thr

25 30 35

gga ctg tgt aat cgg tca tcc tgt ccc ctg gca aat agt cag tat gcc

Gly Leu Cys Asn Arg Ser Ser Cys Pro Leu Ala Asn Ser Gln Tyr Ala

40

45

50

act att aaa gaa gag aaa gga cag tgc tac ttg tat atg aag gtt ata

Thr Ile Lys Glu Glu Lys Gly Gln Cys Tyr Leu Tyr Met Lys Val Ile

55 60 65

gaa cga gcg gct ttt cct cgg cgt ctc tgg gaa cgg gtc cgg ctt agt
Glu Arg Ala Ala Phe Pro Arg Arg Leu Trp Glu Arg Val Arg Leu Ser
70 75 80

					_	ctg Leu				_	_					461
		_			-	cac His		-								509
					_	att Ile	_					_	_	_		557
		_		_	-	aag Lys	_			-				_	-	605
						gct Ala 155										653
_		_		_	_	aaa Lys		-	_			_				701
				_		gac Asp		_	_	_		_	~ ~	_		749
_	-			-		gag Glu	-		-	-	-	-	_	_		797
						gaa Glu										845
_	-		_	_		gag Glu 235	-	_	_		_	_	-	-	-	893
_	_	_	_	_		aaa Lys			_			-	_	-	-	941
_		~	~ ~			aaa Lys			_		_	_			_	989
_	_		_	_		gtg Val	_		_			_	-			1037
		_		_		acc Thr	_	tga *	tttc	cc ct	ttca	agtca	a ttt	atad	ccca	1089
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gag Glu	atg Met	tca Ser 25	gga Gly	ggt Gly	gga Gly	gcc Ala	cct Pro 30	gca Ala	gag Glu	gag Glu	acc Thr	aaa Lys 35	ggc Gly	aca Thr	gct Ala	149
gga Gly	aag Lys 40	gcc Ala	atc Ile	aat Asn	gag Glu	ggg Gly 45	cct Pro	ccc Pro	act Thr	gag Glu	tca Ser 50	gga Gly	aag Lys	cag Gln	gaa Glu	197
aag Lys 55	gca Ala	cca Pro	gcc Ala	gag Glu	gac Asp 60	ggc Gly	atg Met	tca Ser	gca Ala	gaa Glu 65	ctc Leu	cag Gln	Gly	gaa Glu	gca Ala 70	245
aat Asn	gga Gly	tta Leu	gat Asp	gag Glu 75	gtc Val	aaa Lys	gtg Val	gaa Glu	tct Ser 80	cag Gln	agg Arg	gag Glu	gct Ala	ggt Gly 85	ggg Gly	293
aaa Lys	gag Glu	gat Asp	gct Ala 90	gag Glu	gct Ala	gaa Glu	ctt Leu	aaa Lys 95	aag Lys	gag Glu	gat Asp	ggt Gly	gag Glu 100	aag Lys	gaa Glu	341
gag Glu	acc Thr	act Thr 105	gtg Val	ggt Gly	tct Ser	cag Gln	gag Glu 110	atg Met	act Thr	ggc Gly	agg Arg	aaa Lys 115	gaa Glu	gag Glu	acc Thr	389
aaa Lys	tct Ser 120	gaa Glu	ccc Pro	aaa Lys	gag Glu	gct Ala 125	gag Glu	gaa Glu	aag Lys	gag Glu	agc Ser 130	acg Thr	ctg Leu	gcc Ala	tct Ser	437
gag Glu	aag Lys	cag Gln	aag Lys	gct Ala	gag Glu	gag Glu	aaa Lys	gag Glu	gcc Ala	aaa Lys	cct Pro	gaa Glu	tct Ser	Gly ggg	cag Gln	485

135					140					145					150	
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aaa Lys	gag Glu	tgc Cys 185	agc Ser	act Thr	gaa Glu	ccc Pro	aag Lys 190	gag Glu	aag Lys	gct Ala	act Thr	gat Asp 195	gaa Glu	gag Glu	gcc Ala	629
aag Lys	gct Ala 200	gaa Glu	tcg Ser	cag Gln	aag Lys	gct Ala 205	gtt Val	gtg Val	gag Glu	gat Asp	gag Glu 210	gct Ala	aag Lys	gct Ala	gaa Glu	677
	aag Lys															725
gag Glu	gct Ala	gat Asp	gca Ala	aaa Lys 235	gag Glu	gag Glu	gcg Ala	gag Glu	gat Asp 240	gca Ala	gag Glu	gag Glu	gca Ala	gag Glu 245	cca Pro	773
ggc Gly	agt Ser	ccc Pro	agc Ser 250	gaa Glu	gag Glu	cag Gln	gag Glu	cag Gln 255	gac Asp	gtg Val	gaa Glu	aaa Lys	gag Glu 260	cca Pro	gag Glu	821
gga Gly	Gly aga	gca Ala 265	Gly	gtg Val	att Ile	ccc Pro	agc Ser 270	tcc Ser	cca Pro	gag Glu	gag Glu	tgg Trp 275	cct Pro	gag Glu	agc Ser	869
ccc Pro	act Thr 280	Gly	gag Glu	ggg ggg	cac His	aac Asn 285	ctc Leu	agc Ser	aca Thr	gat Asp	ggg Gly 290	ctg Leu	ggt Gly	cca Pro	gac Asp	917
tgt Cys 295	gta Val	gct Ala	tcc Ser	gga Gly	cag Gln 300	acc Thr	agt Ser	cct Pro	tca Ser	gcc Ala 305	agt Ser	gag Glu	tct Ser	tca Ser	ccc Pro 310	965
agc Ser	gac Asp	gtg Val	ccc Pro	cag Gln 315	agt Ser	ccc Pro	cct Pro	gag Glu	tcc Ser 320	cct Pro	tcc Ser	tca Ser	ggg	gag Glu 325	aag Lys	1013
aag Lys	gag Glu	aag Lys	gca Ala 330	cca Pro	gag Glu	cgc Arg	agg Arg	gta Val 335	tca Ser	gcc Ala	cct Pro	gct Ala	cgg Arg 340	ccc Pro	cgg Arg	1061
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gca Ala	gct Ala 360	tcc Ser	ggc Gly	ccc Pro	acg Thr	gcc Ala 365	ttg Leu	ttc Phe	cgc Arg	aac Asn	act Thr 370	aag Lys	gca Ala	gcc Ala	ggg Gly	1157

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ccg gag gat gcg ctg tcc ggg gct gca cag gtt ggc tgt gtt ttt tggPro Glu Asp Ala Leu Ser Gly Ala Ala Gln Val Gly Cys Val Phe Trp150155	1433
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60

282

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agg aga cag ctg tgc tct ccc cac tcc tcc ctc cgg cct cag cac cca 378 Arg Arg Gln Leu Cys Ser Pro His Ser Ser Leu Arg Pro Gln His Pro

cag gtg gcc tct gct ctc ttg gag gcg aag ctg ctc ccc tct cct cca 426 Gln Val Ala Ser Ala Leu Leu Glu Ala Lys Leu Leu Pro Ser Pro Pro 55 65 70

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ttg Leu 145	Gly	agt Ser	tcc Ser	aga Arg	cct Pro 150	cac His	agg Arg	agg Arg	agg Arg	cca Pro 155	Cys	gtg Val	caa Gln	. caa . Gln	agc Ser 160	599
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cac His	aag Lys	aag Lys	ggg Gly 180	Leu	agg Arg	aaa Lys	agt Ser	gaa Glu 185	aac Asn	cca Pro	aga Arg	ggc Gly	ccg Pro 190	ttg Leu	gtc Val	695
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tct Ser	gtg Val	acc Thr	ccg Pro	cgc Arg	agc Ser	acc Thr	gcc Ala	agg Arg	ctg Leu	ggc Gly	ccg Pro	cct Pro	ccc Pro	tcc Ser	cac His	1175

340 345 350 gcc tct gcg gat gca acc aga tgt ctt cct tgc ccg gat tcc cag aag 1223 Ala Ser Ala Asp Ala Thr Arg Cys Leu Pro Cys Pro Asp Ser Gln Lys 360 ctg gag aaa gag tgc cag tct tcc gaa gag tcc atg ggg tct aat tcc 1271 Leu Glu Lys Glu Cys Gln Ser Ser Glu Glu Ser Met Gly Ser Asn Ser 375 380 1319 Met Arg Ser Ile Leu Glu Glu Asp Glu Glu Asp Glu Glu Pro Pro Arg 390 395 gtc ctt tta tac cac gaa cca cgt tcg ttt gaa gta gga atg cta gtc 1367 Val Leu Tyr His Glu Pro Arg Ser Phe Glu Val Gly Met Leu Val 405 410 tgg cat aaa cat aaa aaa tac ccc ttc tgg cca gca gtg gtc aaa agc 1415 Trp His Lys His Lys Lys Tyr Pro Phe Trp Pro Ala Val Lys Ser 420 430 gtc agg cag aga gat aag aaa gca agt gtg cta tac atc gaa gga cac 1463 Val Arg Gln Arg Asp Lys Lys Ala Ser Val Leu Tyr Ile Glu Gly His 435 440 atg aac ccg aaa atg aaa ggt ttc aca gtg tct ctt aaa agt tta aag 1511 Met Asn Pro Lys Met Lys Gly Phe Thr Val Ser Leu Lys Ser Leu Lys 450 455 cac ttt gat tgt aaa gag aaa cag acg ctt ctg aat caa gcc agg gag 1559 His Phe Asp Cys Lys Glu Lys Gln Thr Leu Leu Asn Gln Ala Arg Glu 470 475 gac ttc aac cag gac atc ggc tgg tgt gct ccc tca tca ccg act aca 1607 Asp Phe Asn Gln Asp Ile Gly Trp Cys Ala Pro Ser Ser Pro Thr Thr 485 490 ggg tcc ggt tag 1619 Gly Ser Gly * 500

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<212> DNA

<213> Homo sapiens

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<221> CDS

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<400> 288

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ggtctccatg gctgaggtat ttagggtggg accagccggg tgccggccgg gg	geteceaca 1	L20
ggaagccatg tggcctcagc cgcggcgggg ggcccgggtg ggggacgtgg tt	attgcgtt 1	180
gggccccttc actcctcata c atg ggc cac gcg ctg gcg tgc act Met Gly His Ala Leu Ala Cys Thr $ 1 \qquad \qquad 5 \qquad \qquad 5 $		231
ctc gcc cgc ctg ctc aca ctc aca cac tcc cac tca agc tgg c Leu Ala Arg Leu Leu Thr Leu Thr His Ser His Ser Ser Trp H 15 20	ac cac 2 is His 25	79
acc ctc tgt gca cac gca cac acg tgc aca ctc gta cat aca c. Thr Leu Cys Ala His Ala His Thr Cys Thr Leu Val His Thr H 30 35 40	ac ccg 3 is Pro	27
ctc gct cac gct cac ctc tgc tca tgc ccg ttc aca cac aca cc Leu Ala His Ala His Leu Cys Ser Cys Pro Phe Thr His Thr P: 45 50 55	ca tcc 3 ro Ser	75
tgc ttt aaa ccc atc ctg tct cct gat gat aaa tat gct tgt tc Cys Phe Lys Pro Ile Leu Ser Pro Asp Asp Lys Tyr Ala Cys Se 60 65 70	cg gta 4 er Val	23
cag cag tct tag taa aataaaatgt ctgtcaggcg acaaggagaa agtgo Gln Gln Ser * 75	cacgtt 4	78
gacetttgae eegagggtgg aceteggtee eteceaeeeg agggeateag gte	ccctgcag 5	38
ggggtgaccc ctgagcatgt gaccccatgg gcgtggccac cccactggtg gga	actggccc 5	98
cacetteete tteeetgget etgggetggg ggagetggge tgggggagtt ggg	gctgtctc 6	58
gCCaCaggCCC gggggccagga tgaaaacggac taaaaaaaata aactcttcac ctc	7207 7	1 2

<210> 289

<211> 975

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (393)..(935)

<400> 289

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atggaaaata tggacataag aatttacagt taagaaaagg ctgtaaaagt gtggatgagt	300
gtaagggaca ccaaggaggt tataatggac ttaaccaatg tttgaaaatt accacaagca	360
aaatatttca atgtaataaa tatgtaaaag to atg cat aaa ttt tca aat tca Met His Lys Phe Ser Asn Ser 1 5	413
aat aga cac aag ata aga cat act gaa aat aaa cat ttc aga tgt aaa Asn Arg His Lys Ile Arg His Thr Glu Asn Lys His Phe Arg Cys Lys 10 15 20	461
gaa tgt gac aaa tca ctt tgc atg ctt tca cgc cta act caa cat aaa Glu Cys Asp Lys Ser Leu Cys Met Leu Ser Arg Leu Thr Gln His Lys 25 30 35	509
aaa att cat act aga gag aat ttc tac aaa tgt gaa gag tgt gga aaa Lys Ile His Thr Arg Glu Asn Phe Tyr Lys Cys Glu Glu Cys Gly Lys 40 45 50 55	557
acc ttt aac tgg tcc aca aac ctt tct aaa cct aag aaa att cat act Thr Phe Asn Trp Ser Thr Asn Leu Ser Lys Pro Lys Lys Ile His Thr 60 65 70	605
gga gaa aaa ccc tac aaa tgt gaa gta tgt gga aaa gcc ttt cac caa Gly Glu Lys Pro Tyr Lys Cys Glu Val Cys Gly Lys Ala Phe His Gln 75 80 85	653
tcc tca atc ctt act aaa cat aag ata att cgt act gga gaa aaa ccc Ser Ser Ile Leu Thr Lys His Lys Ile Ile Arg Thr Gly Glu Lys Pro 90 95 100	701
tat aaa tgt gca cac tgt ggc aaa gcc ttt aaa cag tcc tca cac ctt Tyr Lys Cys Ala His Cys Gly Lys Ala Phe Lys Gln Ser Ser His Leu 105 110 115	749
act aga cat aag ata att cat act gaa gag aaa ccc tac aaa tgt gaa Thr Arg His Lys Ile Ile His Thr Glu Glu Lys Pro Tyr Lys Cys Glu 120 125 130 135	797
caa tgt ggc aag gtc ttt aag cag tcc cca acc ctt act aaa cat cag Gln Cys Gly Lys Val Phe Lys Gln Ser Pro Thr Leu Thr Lys His Gln 140 145 150	845
ata att tat act gga ggt cga cgc gac cgc gaa ttc gga tcc tcg aga Ile Ile Tyr Thr Gly Gly Arg Arg Asp Arg Glu Phe Gly Ser Ser Arg 155 160 165	893
gat ctc ttt ttt tgg gtt tgg tgg ggt atc ttc gtc atg taa tagggcg Asp Leu Phe Phe Trp Val Trp Trp Gly Ile Phe Val Met * 170 175 180	942
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gcacg atg gcc tcg tct cag ggg aaa aac gag ctg aaa tta gcc gac Met Ala Ser Ser Gln Gly Lys Asn Glu Leu Lys Leu Ala Asp 1 5 10	167
tgg atg gca act ctg ccg gag agc atg cac agc atc ccc ctc acc aat Trp Met Ala Thr Leu Pro Glu Ser Met His Ser Ile Pro Leu Thr Asn 15 20 25 30	215
tta gcc att cca ggg tct cat gat tcc ttc agc ttc tac att gat gaa Leu Ala Ile Pro Gly Ser His Asp Ser Phe Ser Phe Tyr Ile Asp Glu 35 40 45	263
gcc tct cca gta ggt cct gag cag cca gaa act gtc cag aat ttt gtc Ala Ser Pro Val Gly Pro Glu Gln Pro Glu Thr Val Gln Asn Phe Val 50 55 60	311
tct gtg ttt gga act gtg gcc aaa aag ctc atg cgg aaa tgg tta gcc Ser Val Phe Gly Thr Val Ala Lys Lys Leu Met Arg Lys Trp Leu Ala 65 70 75	359
act cag aca atg aat ttt act ggc cag cta gga gct gga att cgt tat Thr Gln Thr Met Asn Phe Thr Gly Gln Leu Gly Ala Gly Ile Arg Tyr 80 85 90	407
ttt gat ctt cga att tcc acc aag ccc aga gac ccc gac aat gaa ctc Phe Asp Leu Arg Ile Ser Thr Lys Pro Arg Asp Pro Asp Asn Glu Leu 95 100 105 110	455
tat ttt gct cat ggt ttg ttc agt gcc aaa gtc aat gaa ggc ctt gag Tyr Phe Ala His Gly Leu Phe Ser Ala Lys Val Asn Glu Gly Leu Glu 115 120 125	503
gag atc aat gca ttc ctc aca gat cac cat aag gag gta gtg ttc ttg Glu Ile Asn Ala Phe Leu Thr Asp His His Lys Glu Val Val Phe Leu 130 135 140	551
gac ttc aac cac ttc tat ggg atg cag aaa tat cac cat gaa aaa ctg Asp Phe Asn His Phe Tyr Gly Met Gln Lys Tyr His His Glu Lys Leu 145 150 155	599
gtc caa atg ctg aaa gac atc tat gga aat aaa atg tgc cca gcg att Val Gln Met Leu Lys Asp Ile Tyr Gly Asn Lys Met Cys Pro Ala Ile	647

ttt gcc cag gaa gtt agt tta aag tac ctg tgg gag aag gac tat caa Phe Ala Gln Glu Val Ser Leu Lys Tyr Leu Trp Glu Lys Asp Tyr Gln 175 180 185 190	695
gtg ctg gtc ttc tac cat agt cca gtg gct ctg gaa gtg ccc ttt ctc Val Leu Val Phe Tyr His Ser Pro Val Ala Leu Glu Val Pro Phe Leu 195 200 205	743
tgg cct ggg cag atg atg cca gca ccc tgg gcc aac acc aca gac ccc Trp Pro Gly Gln Met Met Pro Ala Pro Trp Ala Asn Thr Thr Asp Pro 210 215 220	791
gag aaa ctg atc cag ttt ctt caa gca tcc atc act gag aga aga aag Glu Lys Leu Ile Gln Phe Leu Gln Ala Ser Ile Thr Glu Arg Arg Lys 225 230 235	839
aag gga tcg ttt ttt ata tct cag gtg gtg ctg acc ccc aaa gct agcLys Gly Ser Phe Phe Ile Ser Gln Val Val Leu Thr Pro Lys Ala Ser240245	887
act gtg gtc aaa ggg gtg gca agt ggc ctc aga gaa aca atc aca gaa Thr Val Val Lys Gly Val Ala Ser Gly Leu Arg Glu Thr Ile Thr Glu 255 260 265 270	935
aga gct ctt cct gcc atg atg cag tgg gtc cgc acg cag aag cca gga Arg Ala Leu Pro Ala Met Met Gln Trp Val Arg Thr Gln Lys Pro Gly 275 280 285	983
gag agt ggc atc aat att gtc act gcc gat ttt gta gaa ctt ggt gac Glu Ser Gly Ile Asn Ile Val Thr Ala Asp Phe Val Glu Leu Gly Asp 290 295 300	1031
ttt atc agc act gtc ata aag ctc aac tat gtc ttt gat gaa gga gaa Phe Ile Ser Thr Val Ile Lys Leu Asn Tyr Val Phe Asp Glu Gly Glu 305 310 315	1079
gcc aac act tga tag cactacttgg agtttccatg aataagatgg agaaagctca Ala Asn Thr * 320	1134
ttgtattagg gcatactatc tgtaaacact ctgatcttcc tattccactg agtctctgaa	1194
gggaataggg ctggtagtgg gtgggaaaaag gggaaaaact gtttcttcag tgattacaat	1254
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<213> Homo sapiens

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	aag Lys								747
	aca Thr								795
	gat Asp				 _	_		 -	843
	gac Asp 235								891
	tct Ser								939
	gac Asp								987
	gcc Ala						_		1035
	cgg Arg								1083
	acc Thr 315						_	-	 1131
	atg Met								1179
	acc Thr								1227
_	tgc Cys								1275
	cgg Arg								1323
	cta Leu 395								1371

															cga Arg	14	119
					gaa Glu 430											14	167
					Gly											15	515
					ctg Leu											15	563
					gag Glu											16	511
					gac Asp											16	559
					atc Ile 510											17	07
					aag Lys											17	'55
					tcc Ser											18	103
					Gly ggg											18	51
					ctg Leu											18	99
					cca Pro 590											19	47
					gtc Val											19	95
					caa Gln											20	43
cag	gaa	ggc	atg	cag	gct	gtc	atg	tcc	agc	gac	ttt	gcc	atc	acc	cgc	20	91

Gln	Glu	Gly 635	Met	Gln	Ala	Val	Met 640	Ser	Ser	Asp	Phe	Ala 645	Ile	Thr	Arg	
	aag Lys 650															2139
	cgc Arg															2187
	gtc Val															2235
	acc Thr															2283
	tcc Ser															2331
	gaa Glu 730			_	_	_					_	_	~ ~	_		2379
	gag Glu															2427
	tac Tyr															2475
	tct Ser															2523
	ctc Leu															2571
	att Ile 810															2,619
	gta Val															2667
	aat Asn															2715
	ctc Leu															2763

860 865 870 ttt ttc ctg tct ctg caa gga act tgt ggg aag tct cta atc tca aaa 2811 Phe Phe Leu Ser Leu Gln Gly Thr Cys Gly Lys Ser Leu Ile Ser Lys 875 880 gct cag aaa att gac aaa ctc ccc cca gac aaa aga aac ctg gaa atc 2859 Ala Gln Lys Ile Asp Lys Leu Pro Pro Asp Lys Arg Asn Leu Glu Ile 895 2907 cag agt tgg aga agc aga cag agg cct gcc cct gtc ccc gaa gtg gct Gln Ser Trp Arg Ser Arg Gln Arg Pro Ala Pro Val Pro Glu Val Ala 910 915 cga cca act cac cac cca gtg tca tct atc aca gga cag gac ttc agt 2955 Arg Pro Thr His His Pro Val Ser Ser Ile Thr Gly Gln Asp Phe Ser 925 930 gcc agc acc cca aag agc tct aac cct ccc aag agg aag cat gtg gaa 3003 Ala Ser Thr Pro Lys Ser Ser Asn Pro Pro Lys Arg Lys His Val Glu 940 945 950 gag tca gta ctc cac gaa cag aga tgt ggc acg gag tgc atg agg gat 3051 Glu Ser Val Leu His Glu Gln Arg Cys Gly Thr Glu Cys Met Arg Asp 955 960 gac tca tgc tca ggg gac tcc tca gct caa ctc tca tcc ggg gag cac 3099 Asp Ser Cys Ser Gly Asp Ser Ser Ala Gln Leu Ser Ser Gly Glu His 970 975 ctg ctg gga cct aac agg ata atg gcc tac tca aga gga cag act gat 3147 Leu Leu Gly Pro Asn Arg Ile Met Ala Tyr Ser Arg Gly Gln Thr Asp 990 995 atg tgc cgg tgc tca aag agg agc cat cgc cga tcc cag agt tca 3195 Met Cys Arg Cys Ser Lys Arg Ser Ser His Arg Arg Ser Gln Ser Ser 1005 1010 3250 ctg acc ata tga gga gctgcagaaa tctgtacaaa ctcaacagag gccacctagt Leu Thr Ile 1020 cactggtcca cataaccett gaccecttet tetteataga ggaaacaatg tgccagtett 3310 attetttet teaacaacet tgactteeat ggaggaagtg etggeeceaa ggggtetgae 3370 acaaagacgg gaaacccagt cggcctctag ttttctgctg ctctcaggca gcacatcttg 3430 caaacagttt ggagaaggag gctgtttttg ttgaatcgag ttctcaaatc ggtttagacc 3490 aaagccattc ttctgaccct ctagataagc gtagcctaca acccagtgcc gtaagtttcc 3550 aagattcaag aagtgtatca acccaggcaa tatctcagga tatggaagtt tctgggttta 3610 tttacccctc agtgcccaga gttaaagttt cagaagagac ttgtgcacat aagggcttca 3670

3730

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gtccaatggc aatttgttca cctctaattt ttataatcat agtttagggt tgtggctaaa	180
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ggattaaaat gtatgggtat accttagaaa ggtgccaaat atggctgggt gtggtggctc	360
atg tct gta atc cca acc cct tgg aag gcc gag gcg ggt ggc tca caa Met Ser Val Ile Pro Thr Pro Trp Lys Ala Glu Ala Gly Gly Ser Gln 1 5 10 15	408
ggt cag gag atc aag acc act ctg gcc aac acg gtg aaa cac cgt ctc Gly Gln Glu Ile Lys Thr Thr Leu Ala Asn Thr Val Lys His Arg Leu 20 25 30	456
cac taa aaatacaaaa tacaaaaaat tacaaaaaata caaagtacaa aaaatacaaa His *	512
aaatacaaaa tactgaaaat actaaaaatt agccgggcat agtggcacgt gcctatagtc	572
CCagCtactt gggaatctgc ggacgcgtgg gtcgacccgg gt	614

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<221> CDS
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ccgatca	tgg	cgga	tggg	cc c	cggt	gcaa	g ag	gcgca	aaac	aag	ccaat	tcc	cagga	aggaaa	a 180
aacgcct	tgg ,	agtca	agaa	at g	agca	ctcg	g ag	cggga	ag	Me	-	_	_	c tgc s Cys 5	233
ttg cca Leu Pro					_	_		_		-	_	_		_	281
ccc ctg Pro Leu								_		_				_	329
ctc cca Leu Pro															377
cca gca Pro Ala 55															425
aaa atc Lys Ile 70					-	_		-	-	_		tga *	agtt	gtc	474
ttttaaa	gaa a	aaact	gaat	t ag	ggagg	gagag	g aaa	aaggg	gaaa	tagg	gagaa	aga a	aagga	aaagt	534
taaattt	gat t	ttttc	ctcca	ag ag	gtttc	ccact	aaa	agggt	tgg	ggad	cagto	gtg a	aagga	agaagg	594
ggagctt	ttt a	acaaa	ataco	ct tt	ggto	ctctc	g aad	cttca	agtg	gcaa	agaa	ıca ç	gggat	caagt	654
tgaatgt	tct d	caggg	gcttt	g ga	atcct	agag	gag	gaaac	caat	caga	agag	jca (gaaat	ggtta	714
tccctgti	tta a	aaata	agco	cc to	cacto	cttta	ı cca	actto	cctt	aaag	gagt	gg a	aggtg	gctggt	774

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<400> 294

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830

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<212> DNA

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<220>

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ggtttcacct	ccatgtgt	tt cattg	gtgca aa	agtggatc	tcttagttg	g tcact	taatt 24	0
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aaccactgtt	atgtacaa	aa aaatg	gcaaa tt	caataaac	tcaaattta	a aataa	ttttt 480	0
aaattaacag	Me	-	n Phe Il		aca aat Thr Asn			8
aga atg gtt Arg Met Val 15	Leu Lys			_	-			6
ttt tat aat Phe Tyr Asr 30								4
ttt tac att Phe Tyr Ile 45								2
ggt ctt ttt Gly Leu Phe								0
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<211> 2388

<212> DNA

<213> Homo sapiens

<220>

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Met Lys Thr Leu Pro Leu Phe Val Cys Ile Cys Ala Leu Ser Ala 10 tgc ttc tcg ttc agt gaa ggt cga gaa agg gat cat gaa cta cgt cac 217 Cys Phe Ser Phe Ser Glu Gly Arg Glu Arg Asp His Glu Leu Arg His 20 aga agg cat cat cac caa tca ccc aaa tct cac ttt gaa tta cca cat 265 Arg Arg His His Gln Ser Pro Lys Ser His Phe Glu Leu Pro His 35 tat cct gga ctg cta gct cac cag aag ccg ttc att aga aag tcc tat 313 Tyr Pro Gly Leu Leu Ala His Gln Lys Pro Phe Ile Arg Lys Ser Tyr 50 55 aaa tgt ctg cac aaa cgc tgt agg cct aag ctt cca cct tca cct aat 361 Lys Cys Leu His Lys Arg Cys Arg Pro Lys Leu Pro Pro Ser Pro Asn 70 aac ccc ccc aaa ttc cca aat cct cac cag cca cct aaa cat cca gat 409 Asn Pro Pro Lys Phe Pro Asn Pro His Gln Pro Pro Lys His Pro Asp 85 90 457 aaa aat agc agt gtg gtc aac cct acc tta gtg gct aca acc caa att Lys Asn Ser Ser Val Val Asn Pro Thr Leu Val Ala Thr Thr Gln Ile 100 105 cca tct gtg act ttc cca tca gct tcc acc aaa att act acc ctt cca 505 Pro Ser Val Thr Phe Pro Ser Ala Ser Thr Lys Ile Thr Thr Leu Pro 115 120 aat gtg act ttt ctt ccc cag aat gcc acc aca ata tct tca aga gaa 553 Asn Val Thr Phe Leu Pro Gln Asn Ala Thr Thr Ile Ser Ser Arg Glu 130 aat gtt aac aca agc tct tct gta gct aca tta gca cca gtg aat tcc 601 Asn Val Asn Thr Ser Ser Ser Val Ala Thr Leu Ala Pro Val Asn Ser 145 150 cca gct cca caa gac acc aca gct gcc cca ccc aca cct tct gca act 649 Pro Ala Pro Gln Asp Thr Thr Ala Ala Pro Pro Thr Pro Ser Ala Thr 165 aca cca gct cca cca tct tcc tca gct cca cca gag acc aca gct gcc 697 Thr Pro Ala Pro Pro Ser Ser Ser Ala Pro Pro Glu Thr Thr Ala Ala 180 185 cca ccc aca cct tct gca act aca caa gct cca cca tct tcc tca gct 745 Pro Pro Thr Pro Ser Ala Thr Thr Gln Ala Pro Pro Ser Ser Ser Ala 195 200 793 cca cca gag acc aca gct gcc cca ccc aca cct cct gca act aca caa Pro Pro Glu Thr Thr Ala Ala Pro Pro Thr Pro Pro Ala Thr Thr Gln 210 215 gct cca cca tct tcc tca gct cca cca gag acc aca gct gcc cca ccc 841 Ala Pro Pro Ser Ser Ser Ala Pro Pro Glu Thr Thr Ala Ala Pro Pro

225 230 235 aca cct cct gca act aca cca gct cca cca tct tcc tca gct cca cca 889 Thr Pro Pro Ala Thr Thr Pro Ala Pro Pro Ser Ser Ala Pro Pro 245 gag acc aca gct gtc cca ccc aca cct tct gca act acc cta gac cca 937 Glu Thr Thr Ala Val Pro Pro Thr Pro Ser Ala Thr Thr Leu Asp Pro 260 265 985 tca tcc gcc tca gct cca cca gag acc aca gct gcc cca ccc aca cct Ser Ser Ala Ser Ala Pro Pro Glu Thr Thr Ala Ala Pro Pro Thr Pro 280 tet gea act aca eea get eea eeg tet tee eea get eea eaa gag ace 1033 Ser Ala Thr Thr Pro Ala Pro Pro Ser Ser Pro Ala Pro Gln Glu Thr 290 295 1081 Thr Ala Ala Pro Ile Thr Thr Pro Asn Ser Ser Pro Thr Thr Leu Ala 305 310 315 cct gac act tct gaa act tca gct gca ccc aca cac cag act act act 1129 Pro Asp Thr Ser Glu Thr Ser Ala Ala Pro Thr His Gln Thr Thr 320 325 330 335 tcg gtc act act caa act act act aca aca cca act tca gct cct 1177 Ser Val Thr Thr Gln Thr Thr Thr Lys Gln Pro Thr Ser Ala Pro 340 345 ggc caa aat aaa att tct cga ttt ctt tta tat atg aag aat cta cta 1225 Gly Gln Asn Lys Ile Ser Arg Phe Leu Leu Tyr Met Lys Asn Leu Leu 360 aac aga att att gac gac atg gtg gag caa tag tatattgt atgttgtaaa 1276 Asn Arg Ile Ile Asp Asp Met Val Glu Gln * 370 375 gtgttctgtc atttacaaga tgtgattcat gagtgcagaa ctaccacctt tcttttagca 1336 ccaatcccaa catgaaatta tattactcag atttaaagca ctatcattaa tctttcaatc 1396 taattattca ccaccacaag acctattaac aagacaaaat gcctctatcc cacaagccag 1456 atgcaggtct ggggttcaaa ataactcttt ggatcctaca gagatagcct actgagggca 1516 1576 gagaaagtcc ttagataaag agagaatatt gtatgggcca tcaaccattt acttttccct gaatgttaga aactacaaaa ccactacctt gtacccccat caaaatccca cctgaaccat 1636 ctaatcctat aaacataaag gggtaaaatt ggaactctcc agatgaacaa agacatctaa 1696 atatctgtag atagaaacat ttatctatct aaatatattg atagacctgt cattgtattg 1756 attaatgaca aaacccttta gataattatc ttccatttta aataaaattt tatttcacaa 1816 1876 atatgagcca agaaagagga aagttgattt gaagtgagga ttagaagtga atgacaataa

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417

aaa gtg aca cat cat att ggg cct tca att ctg gcc tta tac caa aat

Lys Val Thr His His Ile Gly Pro Ser Ile Leu Ala Leu Tyr Gln Asn 70 75 80	
gtg gat aag cat cca gac tat gct tga caaat acaaatagca tccaatatta Val Asp Lys His Pro Asp Tyr Ala * 85 90	469
acacagaatt tecatggttt acaatagcag tggtaateee aaateateet gtgaacgtet	529
cctggaatga ctccatagcc acacagaacc acatatggct tcagatagcc atggccctat	589
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ctctgccatg gggg atg atc agg agg atg att ttc cca ggc ggc tca gcg Met Ile Arg Arg Met Ile Phe Pro Gly Gly Ser Ala 1 5 10	530
aga gta tgg agg acc tca gcc tgg att tgg ggg ccc ttc agg gca gcg Arg Val Trp Arg Thr Ser Ala Trp Ile Trp Gly Pro Phe Arg Ala Ala 15 20 25	578

agt atc tgc agg acc tgg gcc ttg ggg ccc ctt ccc aca gcc agc ctg 626

Ser Ile Cys Arg Thr Trp Ala Leu Gly Pro Leu Pro Thr Ala Ser Leu 30 35 40	
ggg aga ccc cag aca gcc gcc cca ccg gtg aag aac cag gaa gag att Gly Arg Pro Gln Thr Ala Ala Pro Pro Val Lys Asn Gln Glu Glu Ile 45 50 55 60	674
ctc ttt tct cca gct tgg cag ggt ccc aag acc tgt caa ggc ggc gca Leu Phe Ser Pro Ala Trp Gln Gly Pro Lys Thr Cys Gln Gly Gly Ala 65 70 75	722
act ggg aaa ggt cgc gga gct gct cac aga gct ggc gga ggc tca acc Thr Gly Lys Gly Arg Gly Ala Ala His Arg Ala Gly Gly Gly Ser Thr 80 85 90	770
tcg atg cct cag ctg tgg atg agg aac cct gtc tcc ccc gaa cac tgg Ser Met Pro Gln Leu Trp Met Arg Asn Pro Val Ser Pro Glu His Trp 95 100 105	818
cca gcc ttg ctt tga acctgccagg aggagggctg aagacctgga ctcaagggtg Pro Ala Leu Leu * 110	873
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gcg atg ctc aca ttc ttg aat gga agt aga att cct gtc act gag aaa Ala Met Leu Thr Phe Leu Asn Gly Ser Arg Ile Pro Val Thr Glu Lys 30 35 40	146
gca cct cat aaa gga att att aga gat tca acc tgt aag tac ctt cca Ala Pro His Lys Gly Ile Ile Arg Asp Ser Thr Cys Lys Tyr Leu Pro 45 50 55 60	194
gag tgg cag agc tat cag tgc ttt ggg atg gaa tat gca atg gtt Glu Trp Gln Ser Tyr Gln Cys Phe Gly Met Glu Tyr Ala Met Met Val 65 70 75	242

	_	~	_	~	cct Pro	_	_	-	-		-	290
-					ggt Gly							338
					gga Gly							386
					ctg Leu 130							434
	-				ctt Leu							482
_	-	_		-	gga Gly							530
					tta Leu							578
					tgt Cys							626
					gat Asp 210							674
					ctt Leu							722
					aca Thr							770
					ttt Phe							818
					ata Ile							866
					agg Arg 290							914

														acc Thr 315		962
														ctt Leu		1010
														aac Asn		1058
_														tct Ser	_	1106
			~ ~		_	_		_	-			-		cct Pro		1154
														ccg Pro 395		1202
														aag Lys		1250
	-		_			-	-		_					cta Leu		1298
_		_			_	-								ggc Gly		1346
_						-		_	_	_		_		tac Tyr	_	1394
_					_		~ ~						_	ttt Phe 475		1442
_	~		_	_		-	_		-			-	-	ctg Leu	_	1490
		_		_	_		_	_	_	-				aaa Lys	_	1538
														agc Ser		1586
ctg	gtt	gga	aga	atg	tgg	ctc	ttg	gaa	ata	ttt	atg	gct	gca	gtt	tca	1634

Leu Val Gly Arg Met Trp Leu Leu Glu Ile Phe Met Ala Ala Val Ser 525 530 535 540	
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taaacactaa aatcagattt cttcaaaata taaatttgtt ttgattcttt atatttatat	1865
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cgcccgcgcc atg gcc tcc atc tcc gag ctt gcc tgt gtc tac ttg gcc Met Ala Ser Ile Ser Glu Leu Ala Cys Val Tyr Leu Ala 1 5 10	229
ctc att ctg cac gat gac gag gtg atc atc atg gag gtt aat atc aat Leu Ile Leu His Asp Asp Glu Val Ile Ile Met Glu Val Asn Ile Asn 15 20 25	277
acc ctc att aaa gca gcc agt gta aat gtt gaa cct ttt ggc ctg gct Thr Leu Ile Lys Ala Ala Ser Val Asn Val Glu Pro Phe Gly Leu Ala 30 35 40 45	325
tgt ttg gaa agg ccc tgg cca acg tca aca ttg gaa gcc tca tct gca Cys Leu Glu Arg Pro Trp Pro Thr Ser Thr Leu Glu Ala Ser Ser Ala 50 55 60	373
atg tag gggctggtgg acctgctcta gcagctggtg ctgcaccagc aggaggtcct Met *	429
gcccctcca ttgctgctgc ttcagctgag gagaagaaaa tggaagcaaa gaaagaagaa	489
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gaggcctggg cttctgcctg caggtgtctg cggcgaggcc cctagggtac agcccgattt	240
ggcccc atg gtg ggt ttc ggg gcc aac cgg cgg gct ggc cgc ctg ccc Met Val Gly Phe Gly Ala Asn Arg Arg Ala Gly Arg Leu Pro 1 5 10	288
tct ctc gtg ctg gtg gtg ctg ctg gtg gtg	336
aac tac tgg agc atc tcc tcc cgc cac gtc ctg ctt cag gag gag gtg Asn Tyr Trp Ser Ile Ser Ser Arg His Val Leu Leu Gln Glu Glu Val 35 40 45	384
gcc gag ctg cag ggc cag gtc cag cgc acc gaa gtg gcc cgc ggg cgg Ala Glu Leu Gln Gly Gln Val Gln Arg Thr Glu Val Ala Arg Gly Arg 50 55 60	432
ctg gaa aag cgc aat tcg gac ctc ttg ctg ttg gtg gac acg cac aag Leu Glu Lys Arg Asn Ser Asp Leu Leu Leu Val Asp Thr His Lys 65 70 75	480
aaa cag atc gac cag aag gag gcc gac tac ggc cgc ctc agc agc cgg Lys Gln Ile Asp Gln Lys Glu Ala Asp Tyr Gly Arg Leu Ser Ser Arg 80 85 90	528
ctg cag gcc aga gag ggc ctc ggg aag aga tgc gag gat gac aag gtt Leu Gln Ala Arg Glu Gly Leu Gly Lys Arg Cys Glu Asp Asp Lys Val 95 100 105 110	576
aaa cta cag aac aac ata tcg tat cag atg gca gac ata cat cat tta Lys Leu Gln Asn Asn Ile Ser Tyr Gln Met Ala Asp Ile His His Leu 115 120 125	624
aag gag caa ctt gct gag ctt cgt cag gaa ttt ctt cga caa gaa gac	672

Lys Glu Gln Leu Ala Glu Leu Arg Gln Glu Phe Leu Arg Gln Glu Asp 130 135 720 cag ctt cag gac tat agg aag aac aat act tac ctt gtg aag agg tta Gln Leu Gln Asp Tyr Arg Lys Asn Asn Thr Tyr Leu Val Lys Arg Leu gaa tat gaa agt ttt cag tgt gga cag cag atg aag gaa ttg aga gca 768 Glu Tyr Glu Ser Phe Gln Cys Gly Gln Gln Met Lys Glu Leu Arg Ala 160 cag cat gaa gaa aat att aaa aag tta gca gac cag ttt tta gag gaa 816 Gln His Glu Glu Asn Ile Lys Lys Leu Ala Asp Gln Phe Leu Glu Glu 180 caa aag caa gag acc caa aag att caa tca aat gat gga aag gaa ttg 864 Gln Lys Gln Glu Thr Gln Lys Ile Gln Ser Asn Asp Gly Lys Glu Leu 200 gat ata aac aat caa gta gta cct aaa aat att cca aaa gta gct gag 912 Asp Ile Asn Asn Gln Val Val Pro Lys Asn Ile Pro Lys Val Ala Glu 210 215 960 aat gtt gca gat aag aat gaa gaa ccc tca agc aat cat att cca cat Asn Val Ala Asp Lys Asn Glu Glu Pro Ser Ser Asn His Ile Pro His 225 230 ggg aaa gaa caa atc aaa aga ggt ggt gat gca ggg atg cct gga ata 1008 Gly Lys Glu Gln Ile Lys Arg Gly Gly Asp Ala Gly Met Pro Gly Ile 240 245 gaa gag aat gac cta gca aaa gtt gat gat ctt ccc cct gct tta agg 1056 Glu Glu Asn Asp Leu Ala Lys Val Asp Asp Leu Pro Pro Ala Leu Arg 255 aag cct cct att tca gtt tct caa cat gaa agt cat caa gca atc tcc 1104 Lys Pro Pro Ile Ser Val Ser Gln His Glu Ser His Gln Ala Ile Ser 275 cat ctt cca act gga caa gct ctc tcc cca aat atg cct cca gat tca 1152 His Leu Pro Thr Gly Gln Ala Leu Ser Pro Asn Met Pro Pro Asp Ser 295 cac att aaa cac aat gga aac ccc ggt act tca aaa aca gaa tcc ttc 1200 His Ile Lys His Asn Gly Asn Pro Gly Thr Ser Lys Thr Glu Ser Phe 310 cag tcc tct tca gcg ttt aat tcc agg ctc aaa ctt gga cag tag aac 1248 Gln Ser Ser Ser Ala Phe Asn Ser Arg Leu Lys Leu Gly Gln * 320 325 ccagaaattc caaacagatt atactaaagg caggttacca aggacagaag ccggggattc 1308 ccataaaatt ggcaccaatg tgaacacaga gagctcgtaa actgggtcct ggaccttggc 1368 agcacgcttc accgacgtcc tcaaaaccca gaggacacac tcgaaaacga aaagggggcg 1428

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                                                                     120
tgtcagtgac tgaggttcgc tgtgacacag aggggttctc ctggagagct atggcac
                                                                     177
atg ctc cat att aaa agg caa cat gat gct cgc tcc acc cag agg ccc
                                                                      225
Met Leu His Ile Lys Arg Gln His Asp Ala Arg Ser Thr Gln Arg Pro
cgg tcc ccg cca ttc att ccg ctc ccg gcc gag agt cgc tct agc caa
                                                                     273
Arg Ser Pro Pro Phe Ile Pro Leu Pro Ala Glu Ser Arg Ser Ser Gln
tca cct tcc agg ctc agg gcc gag gca ggg cct ctg cct ctt cgg
                                                                     321
Ser Pro Ser Arg Leu Arg Ala Ala Glu Ala Gly Pro Leu Pro Leu Arg
         35
ggg gcc tct ccc tcc ccc tgc ccc tga ttgtg gctgaactgc caccgcttga
                                                                     373
Gly Ala Ser Pro Ser Pro Cys Pro *
     50
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gcc aga aac tct ggc tgc ccc cac ctc ccc aat ggt ccc cat caa gta Ala Arg Asn Ser Gly Cys Pro His Leu Pro Asn Gly Pro His Gln Val 25 30 35	151
ggt aac atc ctg ctg att tta act cct gtg cag ccc tca aat gca caa Gly Asn Ile Leu Leu Ile Leu Thr Pro Val Gln Pro Ser Asn Ala Gln 40 45 50	199
ctg cct ccc att cct gca cag tgc ccc agt tca ggc ctt cac cac ctt Leu Pro Pro Ile Pro Ala Gln Cys Pro Ser Ser Gly Leu His His Leu 55 60 65	247
gtt cct ggg cca ctg ccc aag tct ccc ccg act ggt ggc tgg act tct Val Pro Gly Pro Leu Pro Lys Ser Pro Pro Thr Gly Gly Trp Thr Ser 70 75 80	295
aat act ttt cca act ccc cac tca tta aat cca tcc ccc tct cat taa Asn Thr Phe Pro Thr Pro His Ser Leu Asn Pro Ser Pro Ser His * 85 90 95 100	343
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atg aat aat att aat act aat gcc ccg aga aac aaa ctt cca ata aag Met Asn Asn Ile Asn Thr Asn Ala Pro Arg Asn Lys Leu Pro Ile Lys 15 20 25 30	158

206 gaa ctt ggt aaa gtt tct aaa cat aaa att gcc act aaa aga aca cca Glu Leu Gly Lys Val Ser Lys His Lys Ile Ala Thr Lys Arg Thr Pro 254 cat aaa gaa gat gag gca atg agc tgt tct gaa aat tgt tcg agt gcc His Lys Glu Asp Glu Ala Met Ser Cys Ser Glu Asn Cys Ser Ser Ala cag ggc gac tca ctt cag gat gag tct caa ggg tct cat tct gag tcc 302 Gln Gly Asp Ser Leu Gln Asp Glu Ser Gln Gly Ser His Ser Glu Ser 70 age tet aat eee tee aat eet gaa aet ttg cat gea aag gea aet gat 350 Ser Ser Asn Pro Ser Asn Pro Glu Thr Leu His Ala Lys Ala Thr Asp 80 85 398 tca gtt cta caa ggt tct gaa gga aac aag gtc aag agg aca tcc tgc Ser Val Leu Gln Gly Ser Glu Gly Asn Lys Val Lys Arg Thr Ser Cys 95 100 atg tat ggg gca aac tgc tat agg aag aat cct gtt cat ttt caa cat 446 Met Tyr Gly Ala Asn Cys Tyr Arg Lys Asn Pro Val His Phe Gln His 115 120 ttt agc cat cct ggt gat agt gat tat gga ggt gta caa atc gtg ggc 494 Phe Ser His Pro Gly Asp Ser Asp Tyr Gly Gly Val Gln Ile Val Gly caa gat gag act gat gac cgg cct gaa tgt ccc tat gga cca tcc tgt 542 Gln Asp Glu Thr Asp Asp Arg Pro Glu Cys Pro Tyr Gly Pro Ser Cys 590 tat agg ttg gaa gtt cag tgt cca gtt gaa aaa cac caa ctc agc tag Tyr Arg Leu Glu Val Gln Cys Pro Val Glu Lys His Gln Leu Ser * tttcttctgg tctgcattac agtattttac ctgtcttttt atgaaaagag cacgttctag 650 gaaaggatgg aagattetea aagaaacaac tttccccttc taaggcagat gaaaacctgt 710

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atc ggt tat ggg tat ggc cct tat cat tca gtt tca gaa caa cca cta Ile Gly Tyr Gly Tyr Gly Pro Tyr His Ser Val Ser Glu Gln Pro Leu 35 40 45	264
tac cca caa cca tac caa cca caa tac caa caa	312
catcagtaac tgcaggacat gattattgag gcttgattgg ctgatacgac ttctacatcc	372
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cag gta gaa cag cgg ctg gag ccg gcc aag cgg gca gcc cac aac atc Gln Val Glu Gln Arg Leu Glu Pro Ala Lys Arg Ala Ala His Asn Ile 30 35 40	207
cac aag cgg ctg cag gcc tgt ctg cag ggc cag agc ggg gca gac atg His Lys Arg Leu Gln Ala Cys Leu Gln Gly Gln Ser Gly Ala Asp Met 45 50 55	255

gac aag cgg gtg aag aag ctt ccc ctc atg gct ctg tcc acc acg atg Asp Lys Arg Val Lys Lys Leu Pro Leu Met Ala Leu Ser Thr Thr Met 60 65 70	303								
gct gag agc ctc aag gag ctg gac cct gat tcc agc atg ggg aag gcc Ala Glu Ser Leu Lys Glu Leu Asp Pro Asp Ser Ser Met Gly Lys Ala 75 80 85	351								
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gaa gat agt tta agg aag atg gca ata ata aca aca cat ctt caa tac Glu Asp Ser Leu Arg Lys Met Ala Ile Ile Thr Thr His Leu Gln Tyr 70 75 80	297
cag caa gaa gct att cag aag aat gtt gaa cag tca tcg gat cta cag Gln Gln Glu Ala Ile Gln Lys Asn Val Glu Gln Ser Ser Asp Leu Gln 85 90 95	345
gac cag ttg aat cat ctg ttg aaa tag aatga catgtaagag tgctgtagga Asp Gln Leu Asn His Leu Leu Lys * 100 105	397
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Arg Val Thr Asp Phe Phe Pro His Pro Gly Phe Asn Lys Asp Leu Ser 90 95 100	
gcc aat gac cac aat gat gac atc atg ctg atc cgc ctg ccc agg cag Ala Asn Asp His Asn Asp Asp Ile Met Leu Ile Arg Leu Pro Arg Gln 105 110 115 120	447
gca cgt ctg agt cct gct gtg cag ccc ctc aac ctc agc cag acc tgt Ala Arg Leu Ser Pro Ala Val Gln Pro Leu Asn Leu Ser Gln Thr Cys 125 130 135	495
gtc tcc cca ggc atg cag tgt ctc atc tca ggc tgg ggg gcc gtg tcc Val Ser Pro Gly Met Gln Cys Leu Ile Ser Gly Trp Gly Ala Val Ser 140 145 150	543
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gag aac tga gcccgcg cgccacgggg gcaccttgga agaccaagag aggccgaagg Glu Asn * 250	887
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115

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125

130

Glu Ala Leu Phe Ser Val Arg Pro Ser Leu Ala Pro Asn Arg Met Asp

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Ser Ala Leu Leu Gly Leu Leu Phe Pro Gly Ile Leu Cys Ser Ser Val 20 25 30	
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gat att gtg atg acc cag act cca ctc tcc ctg ccc gtc acc cct gga Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly 25 30 35	150
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cca gac agg ttc agt ggc agt ggg tca ggc act gat ttc aca ctg aaa Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys 85 90 95 100	342
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Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln 105 110 438 cgt ata gag ttt cct tgg act ttt ggc cag ggg acc aag ctg gag atc Arg Ile Glu Phe Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile 120 aaa cga act gtt gct gca cca tct gtc ttc atc ttc ccg cca tct gat 486 Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp 135 140 145 gag cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac 534 Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn 150 155 ttc tat ccc aga gag gcc taa gt acagtggaaa gtggtaaacg gcctccaaac 587 Phe Tyr Pro Arg Glu Ala tggttaaatc cagtaaagtg tcacagagca agacagtaag gacagcacct acgtactcag 647 cagcaaccag aagctgagca aagttgactt atgagatacc acaagtctag gcctgacgaa 707 gtcaaccatt atggacttgg gctgtgtcca atctgaatat agttatacct gggcagagtg 767 gttaaaaggt atagtgtgtc ccctaaattg tatcctaggt ttcaagctcg tagtcacttg 827 cccaggettt ttgtcccttg taggtccttt tttcccaatg ggggacctaa gacactaagt 887 gacgggactc tccaaagtta atgatttaaa acttaaaatc actctctaag ggatcatcag 947 gagttatgaa gtcgatgact aattgttttt gatacgagta tatctgaaaa tgattgaaag 1007 tgtgaattcc tcatggtagg tgagataaac tagtcgttat agtatctagt agatgaccgg 1067 agcatttata gagtagaagt ccgcatactc ccggataatc taccacgaca catgattaga 1127 ctctcgcgat ggtaaacaga tggatgtaaa ctcaatcgtg ggagtaccga aagaggtggc 1187 tatgatgttg acatgatagg gtctaggatg cgtgatcgtg tgacggaatt gtcaaatacg 1247 tgtgaataca catttattgg caatttctgt atgacgtgat atgacgattag cagaggttta 1307

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tgt ctc ctt gga aca ggt cat ggg gat gcc atg gtc atc cag aac cca Cys Leu Leu Gly Thr Gly His Gly Asp Ala Met Val Ile Gln Asn Pro 15 20 25	157
aga tac cag gtt acc cag ttt gga aag cca gtg acc ctg agt tgt tct Arg Tyr Gln Val Thr Gln Phe Gly Lys Pro Val Thr Leu Ser Cys Ser 30 35 40	205
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tac ctg tgt gcc acc agc gtc cac cgg gac cca tga acac tgaagctttc Tyr Leu Cys Ala Thr Ser Val His Arg Asp Pro * 110 115	447
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caa aga aaa gat gaa gaa atg gga tct ctg cag gac cgt gta att Gln Arg Lys Asp Glu Glu Met Gly Ser Leu Gln Asp Arg Val Ile 50 55 60									
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gag aaa ctg agc cta cta gaa gat ttc aaa gac ttc aga gat tcc Glu Lys Leu Ser Leu Leu Glu Asp Phe Lys Asp Phe Arg Asp Ser 80 85 90	-								
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aga aat tot ott oag oat oac oaa gat gac acc aag tac aga acc Arg Asn Ser Leu Gln His His Gln Asp Asp Thr Lys Tyr Arg Thr 115 120 125	Lys								
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caa ccc aaa aaa gag gaa tat ggg agc taa a aaagcaaatg taattt Gln Pro Lys Lys Glu Glu Tyr Gly Ser * 195 200	gtta 626								
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	a Val Met L			ggc acc ttt gc: Gly Thr Phe Ala 30	
				gac cct gag aad Asp Pro Glu Ası 45	
	ı Gly Asn V			gca acc cac tto Ala Thr His Pho	

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cac aga gga gga ggg aag ggg gaa agt agc ctc tct cag cac atg His Arg Gly Gly Ala Gly Lys Gly Glu Ser Ser Leu Ser Gln His Met 10 15 20	281
His Arg Gly Gly Ala Gly Lys Gly Glu Ser Ser Leu Ser Gln His Met	281 329
His Arg Gly Gly Ala Gly Lys Gly Glu Ser Ser Leu Ser Gln His Met 10 15 20 ata aaa aga cct gga tgg gga ggt gga gca gag gcc ttc act cca tca Ile Lys Arg Pro Gly Trp Gly Gly Gly Ala Glu Ala Phe Thr Pro Ser	
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His Arg Gly Gly Ala Gly Lys Gly Glu Ser Ser Leu Ser Gln His Met 10 15 20 ata aaa aga cct gga tgg gga ggt gga gca gag gcc ttc act cca tca Ile Lys Arg Pro Gly Trp Gly Gly Gly Ala Glu Ala Phe Thr Pro Ser 25 30 35 ttt ttt aaa tcc atc ctt caa tat ttt caa gag gaa ggg aaa cca gac Phe Phe Lys Ser Ile Leu Gln Tyr Phe Gln Glu Gly Lys Pro Asp 40 45 50 agg cca aac cac agc ctt cag tgg ggc ttg act tta gtt cta cgg acc Arg Pro Asn His Ser Leu Gln Trp Gly Leu Thr Leu Val Leu Arg Thr	329 377

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ccc	gaga	gga a	aggc	Me				a Lei						a Ph	c ctg e Leu	110
					aaa Lys											158
					ggg Gly											206
					tac Tyr 50											254
					ctg Leu											302
					agt Ser			_								350
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					gcc Ala											446
					aaa Lys 130											494
					tct Ser											542

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gcg agc atg gag gag aca agc acg agg tca gaa ttg gag ctg gca gag Ala Ser Met Glu Glu Thr Ser Thr Arg Ser Glu Leu Glu Leu Ala Glu 5 10 15	284
cag acg gag atg gag gga gaa aag gaa gaa agc ctg gtg gaa ggg gagGln Thr Glu Met Glu Gly Glu Lys Glu Glu Ser Leu Val Glu Gly Glu20253035	332
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				40					45					50		
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cct Pro	agg Arg	gac Asp 70	tcg Ser	cgg Arg	gcc Ala	ccg Pro	ctg Leu 75	agg Arg	gta Val	cag Gln	aag Lys	aat Asn 80	gtg Val	cgt Arg	gac Asp	476
aac Asn	tcc Ser 85	aag Lys	gac Asp	tcg Ser	gag Glu	tac Tyr 90	tgg Trp	cag Gln	gcc Ala	ctg Leu	acc Thr 95	aca Thr	gtg Val	atc Ile	cct Pro	524
tcc Ser 100	tcc Ser	aag Lys	cag Gln	aac Asn	ctc Leu 105	tgg Trp	gat Asp	gcc Ala	ctc Leu	tac Tyr 110	aca Thr	gcc Ala	ttg Leu	gag Glu	aag Lys 115	572
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tct Ser	ctg Leu	gag Glu	cag Gln 135	cag Gln	aac Asn	aca Thr	gag Glu	ctg Leu 140	cag Gln	gcg Ala	cta Leu	ctg Leu	cag Gln 145	cag Gln	tat Tyr	668
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120

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tagtcatact cctattcacc gttctcaact actcatac	atg ccc tgc tct tgt Met Pro Cys Ser Cys 1 5	353
tta cac tgc cgg ttt aca ctg ttt ctc caa gcc Leu His Cys Arg Phe Thr Leu Phe Leu Gln Ala 10	atc aca gct gat atc Ile Thr Ala Asp Ile 20	401
tcc tgg tgc tat cct caa act acc act ctt aac Ser Trp Cys Tyr Pro Gln Thr Thr Thr Leu Asn 25	tcc ctc ttg gat ttg Ser Leu Leu Asp Leu 35	449
tta tat gat ctt tgc cgg cag gca ccc ctc caa Leu Tyr Asp Leu Cys Arg Gln Ala Pro Leu Gln 40 45	tac ttt cac cct gat Tyr Phe His Pro Asp 50	497
gaa gtt cta ttc ttt act ttt ata ctc act ctt Glu Val Leu Phe Phe Thr Phe Ile Leu Thr Leu 55 60	att ctc att ccc att Ile Leu Ile Pro Ile 65	545
ctt atg cca ccc ttt acc tct ccc cag cta tct Leu Met Pro Pro Phe Thr Ser Pro Gln Leu Ser 70 75 80	Pro Pro His Tyr Gln	593
tct cac tgt ctc tct cct agc cat ttc taa t c Ser His Cys Leu Ser Pro Ser His Phe * 90 95	cttctttaa caaacaattg	644
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acc ggc aat ggc cag ggc tgg ccc gcc tgc ccc tac tgc ggc aag gcc Thr Gly Asn Gly Gln Gly Trp Pro Ala Cys Pro Tyr Cys Gly Lys Ala 25 30 35 40	147
ttc cgc cgg ccc tcg gac ctc ttc cgg cac cag cgc atc cac acc ggt Phe Arg Arg Pro Ser Asp Leu Phe Arg His Gln Arg Ile His Thr Gly 45 50 55	195
gag cgg ccc tac cag tgc ccc cag tgt ggc cgg acc ttc aac cgc aac Glu Arg Pro Tyr Gln Cys Pro Gln Cys Gly Arg Thr Phe Asn Arg Asn 60 65 70	243
cac cac ctg gcc gtg cac atg cag acc cac gcc cga ggc cag gtg ggc His His Leu Ala Val His Met Gln Thr His Ala Arg Gly Gln Val Gly 75 80 85	291
cca cac ttc cct gcc gcc ccc gcc cgc cac ggg agc ctg ccc ctg ccc Pro His Phe Pro Ala Ala Pro Ala Arg His Gly Ser Leu Pro Leu Pro 90 95 100	339
tgg ccc agc cgg aag gag ggc tga cctgg caggagccca cagaggaccc Trp Pro Ser Arg Lys Glu Glu Gly * 105 110	391
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160

145

727

775

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cgt tcc ctg cgc atc aac aac cgg ctg cgt acg ctg gcg cct ggc Arg Ser Leu Arg Ile Asn Asn Asn Arg Leu Arg Thr Leu Ala Pro Gly

140

155

135

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aac Asn	aaa Lys 25	tta Leu	aga Arg	gaa Glu	gag Glu	aat Asn 30	aaa Lys	ttt Phe	tgt Cys	gat Asp	gtt Val 35	aca Thr	gtt Val	ctc Leu	ata Ile	328
gat Asp 40	gat Asp	att Ile	gag Glu	gta Val	cag Gln 45	gga Gly	cat His	aaa Lys	att Ile	gtg Val 50	ttt Phe	gct Ala	gca Ala	ggt Gly	tcc Ser 55	376
ccc Pro	ttc Phe	tta Leu	aga Arg	gac Asp 60	caa Gln	ttt Phe	tta Leu	ctg Leu	aat Asn 65	gat Asp	tcc Ser	aga Arg	gag Glu	gtg Val 70	aaa Lys	424
atc Ile	tcc Ser	ata Ile	tta Leu 75	cag Gln	agt Ser	tcc Ser	gaa Glu	gtg Val 80	gly ggg	aga Arg	caa Gln	ttg Leu	ctc Leu 85	tta Leu	tcc Ser	472
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Pro	tct Ser	Glu 170	Asp	Ser	Met	Asp	Met 175	Glu	Asp	Ser	Asp	Ile 180	Gln	Ile	Val	760
Lys	gta Val 185	Glu	Ser	Ile	Gly	Asp 190	Va1	Ser	Glu	Val	Arg 195	Ser	Lys	Lys	Asp	808
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ccc Pro	cag Gln	cac His	tcc Ser	ctg Leu 220	ata Ile	aat Asn	tca Ser	act Thr	gtg Val 225	gaa Glu	aac Asn	aga Arg	gta Val	agt Ser 230	gaa Glu	904

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gac Asp	ctc Leu	aca Thr	gtg Val 395	Asp	ttt Phe	gat Asp	tct Ser	ttt Phe 400	Ala	tgt Cys	aca Thr	aca Thr	gtc Val 405	Thr	gac Asp	1432
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	Asn		gta	.gggg	ctt	catg	ccc	acaa	.ctcg	aa c	tgac	tgac	a at	gtgg	caat	1584

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1

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Gln Lys Gln Gln Ser Trp Lys Pro Pro Asn Val Pro Lys Cys Ser Pro

5

120

223

60

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ccc caa aga tca aac ccc tgc cta gct ccc tac tcg act cct tgt ggt
Pro Gln Arg Ser Asn Pro Cys Leu Ala Pro Tyr Ser Thr Pro Cys Gly
20 25 30 35

gct ccc cat tca gaa ggt tgt cat tcc agt tcc caa agg cct gag gtt Ala Pro His Ser Glu Gly Cys His Ser Ser Ser Gln Arg Pro Glu Val 40 45 50	319													
cag aag cct agg agg gct cgt caa aag ctg cgc tgc cta agt agg ggc Gln Lys Pro Arg Arg Ala Arg Gln Lys Leu Arg Cys Leu Ser Arg Gly 55 60 65	367													
aca acc tac cac tgc aaa gag gaa gag tgt gaa ggc gac tga gcccaga Thr Thr Tyr His Cys Lys Glu Glu Glu Cys Glu Gly Asp * 70 75 80	416													
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ctc Leu 85	acc Thr	gtc Val	ctc Leu	tct Ser	gtc Val 90	tgt Cys	gcc Ala	atc Ile	gcc Ala	acc Thr 95	aat Asn	gga Gly	gcc Ala	gtg Val	cag Gln 100	461
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<220>

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tgg gag atg gtc cag ctg aaa atc ccc agc atc cac aag aaa ggg tgg Trp Glu Met Val Gln Leu Lys Ile Pro Ser Ile His Lys Lys Gly Trp 30 35 40	206
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tct ctc ttc tgg tat gtg caa cac ccc aac aaa gga ctc cag ctt ctc Ser Leu Phe Trp Tyr Val Gln His Pro Asn Lys Gly Leu Gln Leu Leu 55 60 65	429
ctg aag tac aca tca gcg gcc acc ctg gtt aaa ggc atc aac ggt ttt Leu Lys Tyr Thr Ser Ala Ala Thr Leu Val Lys Gly Ile Asn Gly Phe 70 75 80	477
gag gct gaa ttt aag aag agt gaa acc tcc ttc cac ctg acg aaa ccc Glu Ala Glu Phe Lys Lys Ser Glu Thr Ser Phe His Leu Thr Lys Pro 85 90 95	525
tca gcc cat atg agc gac gcg gct gag tac ttc tgt gtt gtg agt gac Ser Ala His Met Ser Asp Ala Ala Glu Tyr Phe Cys Val Val Ser Asp 100 105 110	573
aca gtg ctt gag act gca gga gag ctg aac aca agc ctc ctg aga tgc Thr Val Leu Glu Thr Ala Gly Glu Leu Asn Thr Ser Leu Leu Arg Cys 115 120 125 130	621
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tggaactcaa attccgggt atg cac tca acc tcg gca aag gca cct cgc tgt Met His Ser Thr Ser Ala Lys Ala Pro Arg Cys 1 5 10	232
tgg tca cac ccc gtg agt ttt tgt ggt tta cta att gtc ctc tct gga Trp Ser His Pro Val Ser Phe Cys Gly Leu Leu Ile Val Leu Ser Gly 15 20 25	280

			aat Asn				tga * 35	aaca	cago	tg a	attt	aatt	g ct	tatgo	ttag	3	334
catg	cagt	tg t	taac	tato	ıt ct	gatg	ıtgtg	ago	aaga	tat	gaat	acat	gt t	tccc	tggag	g 3	94
gctg	gatt	tg g	gttat	cago	ıt ct	cggg	gcag	r ttt	gata	aat	tgta	ctaa	tg o	ctgca	atcad	c 4	154
tgtt	tttc	aa a	aggto	caca	ıa aç	gcacg	ıttgt	ggc	tttg	ıgga	aagg	caga	.ga t	aaga	agcaa	a 5	514
agct	ttgt	ga t	agag	gacag	ja aa	caaç	ıgcca	ı tga	aaag	ıgga	agct	acca	aa g	gcaat	ggcat	t 5	574
agcc	aagg	jaa ç	gtgtg	tctt	c ac	aaga	ıtaaç	r tgg	rcaag	gac	cctg	rttga	.gt t	gato	rcttg	t 6	534
gttg	rtttg	ıgt a	agaat	taaa	a at	taag	gatga	gtg	ggtt	ggc	ссса	ıgtgg	rtc (catgo	ctgta	a 6	594
atto	cctc	ac t	ttgg	gagg	ga to	gaggo	aggt	gga	tago	tga	ggtc	aaga	ıgt t	caag	gacca	c 7	754
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						Ile								gtt Val		1	103
agc Ser	caa Gln	cgg Arg	aag Lys	gag Glu 25	gtg Val	gag Glu	cag Gln	gat Asp	cct Pro 30	gga Gly	ccc Pro	ttc Phe	aat Asn	gtt Val 35	cca Pro	1	151
gag Glu	gga Gly	gcc Ala	act Thr 40	gtc Val	gct Ala	ttc Phe	aac Asn	tgt Cys 45	act Thr	tac Tyr	agc Ser	aac Asn	agt Ser 50	gct Ala	tct Ser	í	199
														aag Lys		2	247
														aca Thr		2	295

cag ctc aat aga gcc agc cag tat att tcc ctg ctc atc aga gac tcc Gln Leu Asn Arg Ala Ser Gln Tyr Ile Ser Leu Leu Ile Arg Asp Ser 85 90 95 100	343
aag ctc agt gat tca gcc acc tac ctc tgt gtg gtg aac att cgc cca Lys Leu Ser Asp Ser Ala Thr Tyr Leu Cys Val Val Asn Ile Arg Pro 105 110 115	391
gga aac aca cct ttg gga ctg gaa caa gac ttc agg tca cgc tcg ata Gly Asn Thr Pro Leu Gly Leu Glu Gln Asp Phe Arg Ser Arg Ser Ile 120 125 130	439
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ctt gcg atg ctc ttc aca ttg agt ggg ctg aga gct cag tca gtg gct Leu Ala Met Leu Phe Thr Leu Ser Gly Leu Arg Ala Gln Ser Val Ala 10 15 20	281
cag ccg gaa gat cag gtc aac gtt gct gaa ggg aat cct ctg act gtg Gln Pro Glu Asp Gln Val Asn Val Ala Glu Gly Asn Pro Leu Thr Val 25 30 35 40	329
aaa tgc acc tat tca gtc tct gga aac cct tat ctt ttt tgg tat gtt Lys Cys Thr Tyr Ser Val Ser Gly Asn Pro Tyr Leu Phe Trp Tyr Val 45 50 55	377
caa tac ccc aac cga ggc ctc cag ttc ctt ctg aaa tac atc aca ggg Gln Tyr Pro Asn Arg Gly Leu Gln Phe Leu Leu Lys Tyr Ile Thr Gly	425

aac Asn									473
caa Gln 90									521
gct Ala									569
aac Asn									617
atc Ile									665
agt Ser									713
gtg Val 170									761
cta Leu									809
 agc Ser		_	-	_	-				857
att Ile									905
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ttt Phe							tga *		1043

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gac ccg cag ccc ctc aag gag cag ccc gcc ctc aat gac tcc aga tac Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr 195 200 205	624
tgc ctg agc agc cgc ctg agg gtc tcg gcc acc ttc tgg cag aac ccc Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro 210 215 220	672
cgc aac cac ttc cgc tgt caa gtc cag ttc tac ggg ctc tcg gag aat Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn 225 230 235 240	720
gac gag tgg acc cag gat agg gcc aaa cct gtc acc cag atc gtc agc Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser 245 250 255	768
gcc gag gcc tgg ggt aga gca ggt gag tgg ggc ctg ggg aga tgc ctg Ala Glu Ala Trp Gly Arg Ala Gly Glu Trp Gly Leu Gly Arg Cys Leu 260 265 270	816
gag gag att agg tga gaccagctac cagggaaaat ggaaagatcc aggtagcgga Glu Glu Ile Arg * 275	871
caagactata tccagaagaa agccagagtg gacaaggtgg gatgatcaag gttcacaggg	931
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Trp Ser Leu Ser Pro His Leu Val Thr His Phe Gln Pro Met Gly Val 20 25 30	
agt tgg gaa att cta cac aag atc cta gta gat gta att aca tat aat Ser Trp Glu Ile Leu His Lys Ile Leu Val Asp Val Ile Thr Tyr Asn 35 40 45	443
tca atg gtt ttt gat gat ggg gtt tta aaa tca agt tat tca ata ggt Ser Met Val Phe Asp Asp Gly Val Leu Lys Ser Ser Tyr Ser Ile Gly 50 55 60	491
ggg gtg cag tgg ctc acg cct gta att cca gca ctt tgg gag gcc gag Gly Val Gln Trp Leu Thr Pro Val Ile Pro Ala Leu Trp Glu Ala Glu 65 70 75 80	539
gag ggc aga tca caa ggt cgg gag ttc aag acc agc ctg acc aac atg Glu Gly Arg Ser Gln Gly Arg Glu Phe Lys Thr Ser Leu Thr Asn Met 85 90 95	587
gta aaa ctc cgt ctc tac taa aa attcaaaaat tagccggccg tggtggtgga Val Lys Leu Arg Leu Tyr * 100	640
catctgtaat cccagctact tagggggctg aggcaggaga atcgcttgaa cgggggcagg	700
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cgctgctggg tctcctgctg ctgccgctgc tcgcagagcc caggaaactc tgcccgcagc	240
tt atg acg gtc att aac cag ttt ctg acc aag gac aag gac acc tac Met Thr Val Ile Asn Gln Phe Leu Thr Lys Asp Lys Asp Thr Tyr 1 5 10 15	287

atg gac act gtc aac aga tac cac ctc acg gag ccg gaa aga aac aca Met Asp Thr Val Asn Arg Tyr His Leu Thr Glu Pro Glu Arg Asn Thr 20 25 30	335
tcc tct aaa ctc aag gac tgc gtg acc gac aca atg acc ccc gag gag Ser Ser Lys Leu Lys Asp Cys Val Thr Asp Thr Met Thr Pro Glu Glu 35 40 45	383
aca gag gcc gtc gtg cag caa ctg gaa gaa atc aac aac cag tgt gcc Thr Glu Ala Val Val Gln Gln Leu Glu Glu Ile Asn Asn Gln Cys Ala 50 55 60	431
gac acg ata ctg aag taa caccat ccataggcac ctcgggttcc tgtccaggct Asp Thr Ile Leu Lys * 65	485
gcctgtccca accatgagaa tctgggccca gggccccacc ctccctagct cccgccctgc	545
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aagggccaca agatgaccaa gaacatgagc aagcccaggc acagctgccg ccgcgggcgc	180
aagggccaca agatgaccaa gaacatgagc aagcccaggc acagctgccg ccgcgggcgc ctgaccaaac accaaattc atg tgg gac atg atc cga gag gtg tgt ggt ttc Met Trp Asp Met Ile Arg Glu Val Cys Gly Phe	180
aagggccaca agatgaccaa gaacatgagc aagcccaggc acagctgccg ccgcgggcgc ctgaccaaac accaaattc atg tgg gac atg atc cga gag gtg tgt ggt ttc Met Trp Asp Met Ile Arg Glu Val Cys Gly Phe 1 5 10 gcc ccg tat gag cgg cac gcc atg gtg tta ctc aag gtc tcc aag gac Ala Pro Tyr Glu Arg His Ala Met Val Leu Leu Lys Val Ser Lys Asp	180 232

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tgg ctg tct gtg gtg ttc atc ttt cgt gtg ctg gtg tac gtg gtg gca Trp Leu Ser Val Val Phe Ile Phe Arg Val Leu Val Tyr Val Val Ala 25 30 35	749
gcg gag gag gtg tgg gac gat gag cag aag gac ttt gtc tgc aac acc Ala Glu Glu Val Trp Asp Asp Glu Gln Lys Asp Phe Val Cys Asn Thr 40 45 50 55	797

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		gtg Val														893
		ctc Leu 90														941
		cac His														989
		aag Lys														1037
		aag Lys														1085
		aag Lys														1133
	-	ccc Pro 170				-	_						_		_	1181
		ttc Phe														1229
		ctc Leu	_	_	~			_			_		_	_		1277
		ggc Gly								_		_	_			1325
_	_	tgc Cys														1373
		tct Ser 250	_		_	_	-									1421
	tat Tyr 265	cca Pro	taa *	cct	gcga	agato	cag o	cagat	aaga	at ca	aacaç	ggtco	c cc	cca	catg	1476
aggo	ccaco	cca g	ggaaa	aaaag	gg ca	agggg	gcagt	ggo	catco	cttg	ccgt	tagca	agg g	gtggt	gagga	1536

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85

cage

95

403

407

Tyr Val Gln Pro Gly Cys Glu Ser Pro Cys Glu Pro Arg Cys *

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		cac ctg His Leu 15											100
		aaa gag .ys Glu 30											148
		atc gcc lle Ala											196
	e Ser S	ct ggg Ser Gly											244
		cac agc His Ser											292
-	ı Gln G	gag ctg Slu Leu 95	Lys C	ys Leu	Ser	Gly	Gln	Leu	Asp	Gly	Tyr	Arg	340
	pro P	tc ccg Phe Pro											388
		ctc ctc Leu Leu											436
	Ser I	ctg ctg Leu Leu	Gly I										484
		ctg cag Leu Gln											532

						gtc Val										580
						gag Glu										628
						gtg Val										676
						ttt Phe 225										724
						ggg Gly										772
						ggc Gly										820
						gtg Val										868
						ccc Pro										916
_				_		ctg Leu 305										964
						ttc Phe								_	_	1012
	_	_		_	-	ctc Leu	_	-			_					1060
						cat His										1108
						cct Pro										1156
						tcc Ser 385										1204
ctc	cgc	ctg	ccg	cct	ctg	cac	cca	cct	cct	gat	ctc	agg	ttc	tga	agg	1252

Leu Arg Leu Pro Pro Leu His Pro Pro Pro Asp Leu Arg Phe * 395 400 405

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	c ctg gta tct gta gat ggc tat atg aac atg cag ctt gca r Leu Val Ser Val Asp Gly Tyr Met Asn Met Gln Leu Ala 10 15	584
•	a ttc ata aat gag gca ttg cct gga cat cta ggt gaa gtt u Phe Ile Asn Glu Ala Leu Pro Gly His Leu Gly Glu Val 25 30 35	632
	g tgt aat aat gtc ctt tat atc aga gat gtg gaa gaa gag g Cys Asn Asn Val Leu Tyr Ile Arg Asp Val Glu Glu 40 45 50	680
gaa atg ggg Glu Met Gly	g aaa tga gtgaatagca tcttttgaag aggatttttt aaatatgtat y Lys * 55	735
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Asn 10	Asn	Val	His	Thr	Ser 15	Leu	Ser	His	Val	Gln 20	Asn	Gly	Ala	Pro	Phe 25	
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											gac Asp					254
											gaa Glu					302
		_	-					_			gga Gly 85	_		_		350
											agc Ser					398
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											tgt Cys 165					590
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gaa gat tca aaa cca caa gat agg cat ttt gta aga aag gat gtt gtc Glu Asp Ser Lys Pro Gln Asp Arg His Phe Val Arg Lys Asp Val Val	210

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			gtt Val													978
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			aaa Lys													1170
			gct Ala													1218
			caa Gln 375													1266
			att Ile													1314
			caa Gln													1362
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			caa Gln													1458
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			atg Met													1554

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tct gcc atg ttg tca att gag ttc tgg tcc caa ggg agg Ser Ala Met Leu Ser Ile Glu Phe Trp Ser Gln Gly Arg 320 325 330	g Trp Arg Gln
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ggg cag gcc atc cga aag aag att gcc aac ggc act gtg aag aga aaa Gly Gln Ala Ile Arg Lys Lys Ile Ala Asn Gly Thr Val Lys Arg Lys 65 70 75	240
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Met Lys Ser Cys Gln Lys Met Glu

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					aac Asn											364
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					cat His 110					tag * 115	cgct	ctta	ita g	gcago	cac	510
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Gly																160
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						gac Asp 45						_	-		_	256
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-						aac Asn		_	_		~ ~		9		_	400
	_				_	ctg Leu			-	-						448
						aga Arg 125										496
						tcc Ser										544
						gtc Val										592
						aag Lys										640
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_					_	tcc Ser	-	_					-		_	784
			-			ctt Leu										832
		_				gca Ala										880
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ctg gaa ctg atg ctg ctg tgg tgg tca ggg ttc agt gag cag gag gaa Leu Glu Leu Met Leu Leu Trp Trp Ser Gly Phe Ser Glu Gln Glu Glu 10 15 20 25	160
gga ctt ggt gtt tac ccc ttg ttt acc cct ttc ctt ggc ttc ctt cca Gly Leu Gly Val Tyr Pro Leu Phe Thr Pro Phe Leu Gly Phe Leu Pro 30 35 40	208
tgc agg cca ccc tgt gac ccc gtg gtg gcc ccc tct gga acc aag agc Cys Arg Pro Pro Cys Asp Pro Val Val Ala Pro Ser Gly Thr Lys Ser 45 50 55	256
tgc cga ctt cca gca gca cac aca gga tca gtg ctg ggg cca tct gtg Cys Arg Leu Pro Ala Ala His Thr Gly Ser Val Leu Gly Pro Ser Val 60 65 70	304
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His

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373

433

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His Asp Val H	cat cgt gct ctt His Arg Ala Leu 260		aga aggacgtctt	cttcgagaag	936
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_		_	_		aga Arg	_	_	_	_			-				871
-			-		agt Ser			_			-	_	-	_		919
					gtg Val 220											967
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_		_			gag Glu	_	-	-	-							1303
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_		-		-	aag Lys			_	_	-			-	_		1399
	-	-			gtt Val 380	_	_	_		_	_					1447

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